CLINICAL SCIENCE

Chest computed tomography findings in severe influenza pneumonia occurring in neutropenic cancer patients

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OBJECTIVE: To describe the chest computed tomography findings for severe influenza H1N1 infection in a series of hospitalized neutropenic cancer patients.

METHODS: We performed a retrospective systematic analysis of chest computed tomography scans for eight hospitalized patients with fever, neutropenia, and confirmed diagnoses of influenza H1N1. The clinical data had been prospectively collected.

RESULTS: Six of eight patients (75%) developed respiratory failure and required intensive care. Prolonged H1N1 shedding was observed in the three mechanically ventilated patients, and overall hospital mortality in our series was 25%. The most frequent computed tomography findings were ground-glass opacity (all patients), consolidation (7/8 cases), and airspace nodules (6/8 cases) that were frequently moderate or severe. Other parenchymal findings were not common. Five patients had features of pneumonia, two had computed tomography findings compatible with bronchitis and/or bronchiolitis, and one had tomographic signs of chronicity.

CONCLUSION: In this series of neutropenic patients with severe influenza H1N1 infection, chest computed tomography demonstrated mainly moderate or severe parenchymatous disease, but bronchiolitis was not a common feature. These findings associated with febrile neutropenia should elicit a diagnosis of severe viral infection.

KEYWORDS: H1N1; Viral pneumonia; Neutropenia; Cancer; Computed tomography.

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INTRODUCTION

Respiratory infections are a frequent cause of fever in neutropenic patients with cancer and are associated with significant morbidity and mortality. In these patients, lower respiratory tract infections are usually attributed to bacterial and fungal agents (1). Respiratory viral infections are not frequently considered as a diagnosis, except for cytomegalovirus and herpesvirus in patients with bone marrow transplants (2). However, influenza infection may occur among cancer patients, especially during influenza season, with high rates of fatality.

From April through September 2009, during the fall/winter, the southern hemisphere experienced the first wave of the influenza A H1N1 (H1N1) virus, and by the end of December 2009, over 1,600 H1N1-related deaths had been reported in Brazil (3,4). This pandemic resulted in the hospitalization of severely ill cancer patients in Brazil as well as in other geographic regions of the southern hemisphere (5). Despite the use of the H1N1 vaccine and other efforts to control the pandemic, recent reports found that the H1N1 virus circulated in the northern hemisphere during the flu season of 2010-2011 (6).

Recently, several reports have highlighted pulmonary imaging findings for the H1N1 virus (7-10). However, data describing the computed tomography (CT) findings of pulmonary involvement in immunosuppressed patients are scarce (11,12). In fact, little overall information on imaging findings related to viral infection in neutropenic patients is available. To our knowledge, CT findings of the H1N1 virus in this group of patients have not been

No potential conflict of interest was reported.

described. The aim of this study was to describe the chest CT findings of confirmed H1N1 virus in a small series of neutropenic febrile patients with hematologic malignancies and solid tumors.

MATERIALS AND METHODS

Patients

We retrospectively evaluated the chest CTs of eight hospitalized neutropenic cancer patients with a confirmed diagnosis of H1N1 between July 2009 and August 2009. Clinical data were prospectively collected using a standardized case report form that included demographic data, clinical presentation, comorbidities, use of immunosuppressive therapies, time course of acute illness, need for intensive care, oseltamivir treatment, advanced life support, and in-hospital mortality.

Cancer patients with a fever (>37.8℃), respiratory influenza-like illness, neutrophil count below 1000/mm^3 at presentation, and who received a chest CT scan during hospitalization were included. The H1N1 diagnosis was confirmed by at least one of the three following assays: indirect immunofluorescence (IFI), real-time RT-PCR (rRTPCR), or cell culture, and the diagnoses fulfilled the World Health Organization case definitions (13). Viral shedding was evaluated in three mechanically ventilated patients by collecting sequential respiratory samples at different time points after the onset of illness (3). The duration of viral shedding was considered to be the time from the initial onset of symptoms to the last H1N1-confirmed sample.

CT imaging

Chest CT was performed on a Philips Brilliance 6-slice CT Scanner (Philips Systems, Netherlands). For eight patients (three with follow-up CT scans), 11 standard chest CT studies were retrospectively reviewed. The imaging parameters were as follows: 120 kVp, automatic mA adjustment, 2-mm slice thickness, and 2.5 mm of reconstruction. Intravenous contrast was not used. The studies were performed using a standard (not high-resolution) algorithm.

CT analysis

CT images were reviewed for consensus by two thoracic radiologists with 12 and 21 years of experience in pulmonary imaging, respectively. The independent readers recorded the presence of the following findings: consolidation, ground-glass opacities (GGOs), airspace nodules, centrilobular nodules, interlobular septal thickening, and peribronchovascular interstitial thickening, as defined by the Fleischner Society (14). Bronchial wall thickening is not defined in this glossary of terms, so we used the criteria proposed by Shiley et al. (15). Among patients with centrilobular nodules, the presence or absence of a tree-in-bud appearance was also noted. The lobes affected by these findings were recorded. The extent of consolidation, GGOs, and nodules was graded as mild (<25%), moderate (25-75%), or severe (>75%), depending on the percentage of the lobe affected (11). The findings were categorized according to their distribution as diffuse, central, peripheral, or having no specific distribution, as well as by their predominance in the upper, middle, or lower third of the lungs.

The three following patterns of disease were recorded based on pulmonary findings and their distribution: (1) no imaging findings associated with pulmonary infection; (2) direct findings of bronchitis and/or bronchiolitis characterized by bronchial wall thickening and centrilobular opacities (including the tree-in-bud pattern); and (3) predominant findings of pneumonia characterized by areas of consolidation and/or GGOs (15). The crazy-paving pattern was characterized by thickened septa superimposed on a background of GGO. Fibrosis was characterized by irregular linear opacities and bronchiectasis. Pleural effusion was recorded as small, moderate, or large.

RESULTS

The eight patients in our study population were four women and four men whose ages ranged from 4 to 65 years (mean, 15.5 years). The included patients had no comorbidities other than hematological or solid malignancies. The main clinical characteristics, neutrophil count, and outcomes are shown in Table 1. Hematologic cancer occurred in 75% of the patients (n = 6). All patients had received corticosteroid or chemotherapy in the previous 30 days. Six patients (75%) developed respiratory failure and required intensive care, and four of them needed invasive mechanical ventilation. The duration of H1N1 shedding in the three mechanically ventilated patients was 23, 44, and 63 days. All patients received antiviral therapy (oseltamivir), and four received double doses. Five patients received corticosteroids during treatment of the viral infection. Overall hospital mortality was 25% (2/8 patients). The two deaths were due to refractory hypoxia secondary to pulmonary alveolar hemorrhage and acute respiratory distress syndrome, respectively.

Initial CT was performed at a median of 5.5 days (range 4-32) after the onset of symptoms. GGO was seen in all cases (Figure 1) and was severe in three patients, moderate in four, and mild in one. The overall distribution of GGO was diffuse in five patients. In the remaining three patients, the GGO distribution was patchy. Consolidation (7/8 cases) and airspace nodules (6/8 cases) were also common findings. Consolidation was typically moderate with a diffuse and heterogeneous distribution in six patients (Figure 2) and a lobar (non-segmental) distribution in one. The extent of airspace nodules was mild in four of six cases, moderate in one case, and severe in one. The tree-in-bud pattern, interlobular septal thickening, peribronchovascular interstitial thickening, and airway wall thickening were each seen in two patients on the initial scans (Figure 3). The tree-in-bud pattern was severe in one patient and mild in another. It was most pronounced in the peripheral regions and was associated with airway wall thickening. Interlobular septal thickening was severe and diffuse in one patient, while in another, it was moderate and predominantly in the lower lobes. Peribronchovascular interstitial thickening occurred preferentially in the lower lobes and was intense in one patient and mild in another. The most frequent combination of findings was consolidation and GGO. This combination occurred in seven of eight patients and was diffuse and heterogeneous in six patients (Figure 2).

Five patients had features of pneumonia, two had CT findings compatible with bronchitis and/or bronchiolitis, and one had tomographic signs of chronicity (irregular linear opacities and bronchiectasis). One patient with pneumonia had predominant findings of thickened septa

Table 1 - Summary of the clinical characteristics of the patients.

Patient	Sex/ age	Fever	Headache	Malaise	Cough	Purulent sputum	Hemoptoic	Dyspnea	Fever (days)	Respiratory symptoms (days)	Neutrophil count - Neutrophils/mm^3	MV	Outcome
1	M/7	Yes	No	Yes	Yes	Yes	No	Yes	2	2	198	No	Discharged
2	M/10	Yes	No	No	Yes	No	No	No	3	4	38	Yes	Died
3	F/8	Yes	No	No	Yes	No	No	No	4	4	22	No	Discharged
4	F/15	Yes	Yes	No	Yes	No	No	Yes	1	1	27	No	Discharged
5	F/4	Yes	No	No	No	No	No	Yes	10	2	2	No	Discharged
6	F/65	Yes	No	Yes	Yes	Yes	Yes	Yes	2	2	950	Yes	Discharged
7	M/7	Yes	No	Yes	Yes	No	No	Yes	1	1	3	Yes	Discharged
8	M/8	Yes	Yes	Yes	Yes	No	Yes	Yes	8	8	284	Yes	Died

Y: yes. N: no. MV: mechanical ventilation. No patient exhibited myalgia, arthralgia, conjunctivitis, coryza, sore throat, diarrhea, abdominal pain, nausea, or vomiting.

superimposed on a background of GGO and focal areas of consolidation creating a crazy-paving pattern (Figure 4). Of the five patients with pneumonia, lower-third predominance was observed in four with a cranio-caudal distribution. Of those five patients, peribronchial (central) distribution was noted in one and peripheral distribution was noted in one, while three had no specific axial distribution. In the two patients with bronchitis and/or bronchiolitis, the findings were diffuse (without predominant cranio-caudal or axial distribution). Upper-third predominance was noted in the patient with signs of chronicity. No patient had a normal CT appearance. The dominant CT findings are presented in Table 2. Pleural effusion was present in only two patients and was small in both. Pleural effusion was unilateral in one patient and bilateral in the other.

Three patients underwent follow-up CT. CT scans of the patient with the crazy-paving pattern in the first CT showed irregular linear opacities and ectatic bronchioles, as well as mild areas of consolidation and GGOs. The time between the initial and follow-up CT was 25 days. The two other patients had pneumonia on initial CT. One patient showed complete resolution of the parenchymal abnormalities in the second CT scan, which occurred 14 days later. In the other patient, the CT scans demonstrated increasing areas of consolidation and the partial resolution of GGOs and airspace nodules. The interval between the initial examination and follow-up CT was 15 days. All three patients survived.

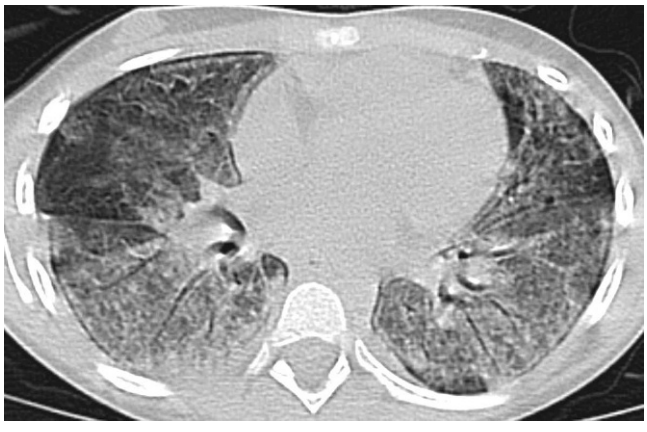

Figure 1 - An 8-year-old girl with a confirmed diagnosis of H1N1 and respiratory failure requiring non-invasive ventilation. Computed tomography scans acquired 4 days after the onset of clinical symptoms show severe and diffuse ground-glass opacities without specific distribution in the lungs.

DISCUSSION

We evaluated the chest CT findings and clinical features of severe pandemic H1N1 virus in eight neutropenic patients. Our findings demonstrate that neutropenic patients with H1N1 infection frequently present diffuse and moderate or severe parenchymatous involvement. To our knowledge, this is the first study to evaluate radiologic features in this population. Pneumonia is the most common infection in febrile neutropenic patients, and CT is the imaging method of choice for guiding the investigation of the lung parenchyma, with high sensitivity in the detection of infiltrates. Viral infection, such as by influenza, parainfluenza, adenovirus, or respiratory syncytial virus, is one common cause of lower respiratory tract infections in neutropenic patients (16). In our series, the most common CT findings associated with pandemic influenza (H1N1) were GGO (all patients), consolidation (7 of 8 patients), or a mixture of GGO and consolidation. Consolidation and GGO were bilateral, diffuse, and heterogeneous in all but one

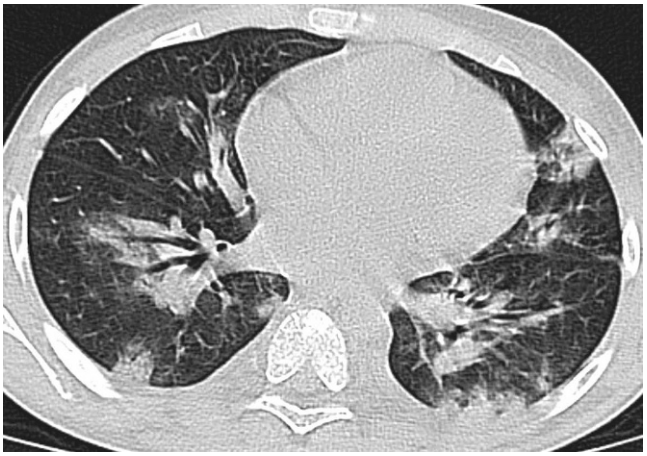

Figure 2 - A 10-year-old boy with a confirmed diagnosis of H1N1. Computed tomography images performed 4 days after the onset of the symptoms demonstrate moderate peribronchovascular and subpleural consolidation predominant in the lower lobes. The boy developed respiratory failure and received mechanical ventilation for 19 days. The duration of viral shedding in this patient was 23 days, and he died 30 days after the onset of clinical symptoms.

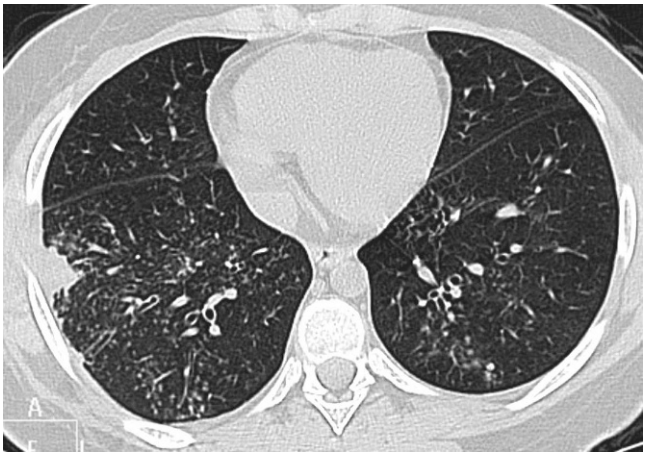

Figure 3 - A 15-year-old girl with mild respiratory symptoms and a confirmed diagnosis of H1N1. A computed tomography scan performed at the carina level shows centrilobular nodules and a tree-in-bud pattern heterogeneously distributed through the lungs, as well as a pleural-based consolidation in the right lower lobe. The girl recovered without the need for admission to the Intensive Care Unit.

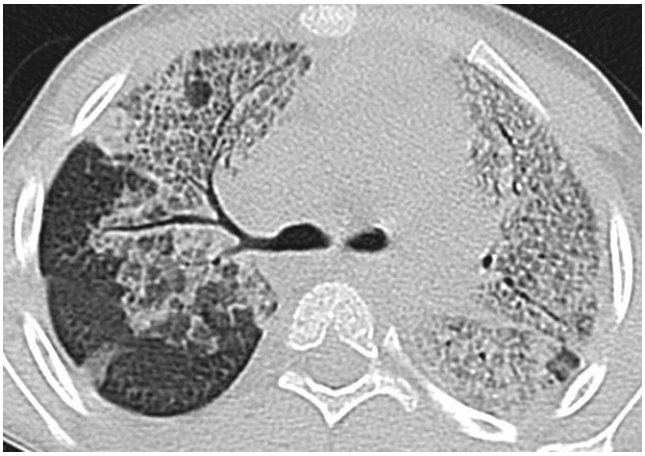

Figure 4 - A 7-year-old boy with respiratory failure and with a confirmed diagnosis of H1N1. A computed tomography scan performed 5 days after the onset of symptoms shows severe ground-glass opacity superimposed on a background of thickened septa charactering a crazy-paving pattern.

patient, who had lobar consolidation. Consolidation, GGO, or a mixture of the two are the findings most frequently seen in influenza infections, regardless of whether they are related to the H1N1 subtype (7,9,15,17,18). Airspace nodules were the third most common finding in our study; however, they are not common in the literature as a viral pneumonia finding, which is likely because some authors interpret airspace nodules as focal areas of consolidation (18,19). The tree-in-bud pattern and airway wall thickening were present in only one-quarter of our patients, although these findings are frequently observed in viral infection, whether of the H1N1 subtype or not (15,20). One patient in our study showed the crazy-paving pattern. This finding was previously described in immunocompetent patients (21,22). Another patient showed signs of chronic disease with irregular linear opacities and bronchiectasis. A CT scan was obtained for this patient 32 days after the onset of the symptoms. Although imaging findings are not frequently seen in viral pneumonia, this patient had prolonged influenza shedding. As in previous studies, pleural effusion was not a significant feature (20,23).

Although they occur with variable frequency, consolidation, GGO, bronchial wall thickening, and the tree-in-bud pattern are the most frequent CT findings associated with infection by the H1N1 virus, regardless of the host's immune status. However, when we evaluated patterns, pneumonia was the most common (5 of 8 patients). In two patients, the set of findings resembled organizing pneumonia, with GGO and consolidation predominantly distributed in the subpleural and basal regions and associated with peribronchovascular thickening. Direct signs of bronchiolitis characterized by bronchial wall thickening and centrilobular opacities (mainly exhibiting the tree-in-bud pattern) were not a frequent finding in our series (2 patients). The number of cases of bronchiolitis, however, may be higher because we did not assess indirect signs of small airway disease, observed only at expiration scans (21,24). The tree-in-bud pattern was observed in two of three patients with hematologic malignancies and influenza infection studied by Oikonomou et al. (20), and bronchial wall thickening was the most common finding in immunosuppressed patients with H1N1 infection described in a study by Elicker et al. (12). In that study, the authors observed mainly bronchial involvement without diffuse and severe lung disease. These differences may be because our series comprised only hospitalized patients, most of whom were critically ill and profoundly immunosuppressed. The source of immunosuppression in our population was diverse; all patients had recently received corticosteroids and chemotherapy and were neutropenic. Regarding neutropenia, it is interesting to note that neutrophils play a key role in the pathogenesis of acute lung injury (25), and their depletion could play a protective role in different experimental pathologic conditions (26). However, recent data highlight the role of neutrophil function in limiting the extent and severity of lung injury in experimental influenza infection (27,28). Studies demonstrate that neutrophils in influenza infection act mainly to control the viral replication process and reduce the risk of severe lung injury (27,28). Interestingly, some of our neutropenic patients experienced not only severe lung disease but also prolonged viral shedding despite the use of oseltamivir.

Studies (21,29) have connected the duration of illness and imaging findings observed in the early stages of diffuse alveolar damage with ground-glass opacities and consolidation. In later stages, typical findings of organization and fibrosis including interstitial fibrosis and bronchiolitis obliterans, with or without evidence of organizing pneumonia, were noted. In most cases, pulmonary opacities secondary to H1N1 infection regress during convalescence. Even in cases with benign evolution, consolidations may occasionally progress to linear opacities (parenchymal bands) that likely represent organizing pneumonia. Air trapping, which represents small-airway disease, may also be clinically and radiologically identified in certain cases.

Bacterial pneumonia is the most common cause of hospitalization in immunosuppressed cancer patients with pulmonary symptoms. However, viral pneumonia and invasive fungal infection should be excluded or treated if

Table 2 - Summary of the computed tomography findings of the eight initial computed tomography scans.

Patient	GGO	Consolidation	Airspace nodules/tree-in-bud	Centrilobular nodules	Septal thickening	Peribronchovascular thickening	Airway wall thickening	Pattern
1	+++	+	-	-	+++	-	-	Pneumonia (**)
2	++	++	+	-	++	++	-	Pneumonia(*)
3	+++	++	+	-	-	-	-	Pneumonia
4	++	+	++	+++	-	-	+++	Bronchiolitis
5	++	++	+	-	-	-	-	Pneumonia
6	+++	++	++	-	-	+++	-	Pneumonia(*)
7	++	+	-	-	+ (†)	-	-	Fibrosis
8	+	-	+	+	-	-	+++	Bronchiolitis

(*) The findings were predominantly distributed in the subpleural and basal regions and were associated with peribronchovascular thickening; (**) thickened septa superimposed on a background of ground-glass opacity (GGO) and focal areas of consolidation charactering a crazy-paving pattern; (†) septal thickening was irregular and associated with irregular opacities and bronchiectasis.

they are suspected. Other differential diagnoses include alveolar hemorrhage, drug-induced pulmonary injury, and oncologic disease progression. Influenza pneumonia may present with a broad variety of CT patterns, none of which are specific for diagnosis. Although the CT findings of pulmonary H1N1 infection are frequently similar to the imaging findings of other diseases, extensive or diffuse GGO and consolidation patterns (mainly in a peribronchovascular or subpleural distribution) in an appropriate clinical and epidemiological context should suggest the possibility of H1N1 infection. Less typical tomographic presentations have a broad differential diagnosis. A specific discussion of each of these patterns and their causes are beyond the scope of this work.

If the clinical setting or imaging studies are not compatible with H1N1, or if the response to treatment is not adequate, an alternative investigation must be initiated. Alveolar hemorrhage is suspected early in the course of the disease, usually clinically. Drug-induced pulmonary injury is also a possibility if a drug with this potential risk profile has been used, and some clues in the CT scan may help with an accurate evaluation. Oncologic disease progression is always a possibility; however, if clinical and CT data are not suggestive, an invasive diagnosis such as lung biopsy is necessary.

This study has certain limitations. It was a small series and an observational study that did not interfere with patient care. Moreover, the observational design did not allow us to use specific imaging and clinical protocols, implying a variation in the time from initial symptoms to the acquisition of chest CT scans.

In conclusion, in this series of neutropenic patients with severe H1N1 viral infections, chest CT demonstrated that pulmonary disease was characterized mainly by diffuse and moderate or severe parenchymatous disease, and bronchiolitis was not a common feature. Viral infection should be considered in the differential diagnosis of febrile neutropenic patients with these findings, especially during flu season. Further studies should confirm this observation in a larger series of patients.

AUTHOR CONTRIBUTIONS

Rodrigues RS, Marchiori E, Bozza FA, Soares M, and Salluh JIF conceived and designed the study, conducted and participated in data analysis, and drafted the manuscript. Pitrowsky MT, Velasco E, Soares M, and Salluh JIF were responsible for the acquisition of clinical data. Rodrigues RS and Marchiori E were responsible for the collection of radiological data. All authors read and approved the final version of the manuscript.

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