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Case Report

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Case Report of a Man with HSV-1 Infection: Pulmonary and Encephalic Disease

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Introduction

Lower respiratory tract diseases are one of the most important causes of morbidity and mortality and their incidence is constantly increasing: the WHO has estimated that in 2020 these diseases will be established as the third cause of death in the world [1]. Iinfectious etiology represents the main cause. The most important viral pathogens involved in the pathogenesis of these diseases are the Orthomyxoviruses and Paramyxoviruses and this correlation makes them frequent object of research and continuous diagnostic investigation [2]. Herpesviruses are also considered as the etiological agent of numerous diseases, especially respiratory and neurological one. These viruses are often underrated in clinical-diagnostic-laboratory investigations: among these, HSV-1 is rarely considered in the management of critically ill patients in the Intensive Care Units [3-5]. This lack of clinical interest could be justified by two main reasons: both because the pathogenic role of these viruses is not yet completely known and because of a poor presence of consolidated epidemiological studies in Literature. HSV-1 is a ubiquitous pathogen with a seroprevalence in adults of 52-85% [1,6,7]. Primary infection, which often occurs during childhood, runs asymptomatic in most cases, although sometimes it can occur with gingivostomatitis. Less common clinical onset are meningitis, encephalitis [8,9], hepatitis [10] and pneumonia [11] and the age of onset is indifferent, affecting both children and adults.

After the first contact, due to its neurotropism, the virus remains in a state of latency into the neuronal cells, being able to reactivate as a result of numerous trigger factors: fever, stress, trauma and immunosuppression states. It is not clear whether HSV-1 is primarily responsible for organ failure or if its presence in various biological samples is due to its reactivation: in this regard, both the depression of the immune system and the presence of concomitant diseases play a crucial role. Recently, the role of HSV-1 in the onset of respiratory diseases of critically ill patients has been strongly revalued: it has been established that, starting from a reactivation of HSV-1 in the oropharynx, the infection progresses towards the lower airways of the patients supported by mechanical ventilation [12]. This consideration does not clarify the controversial role of this virus and the difficulty that remains is to differentiate a primary herpetic bronchial pneumonia caused by HSV-1 compared to a migration of the same virus from the oropharynx to the lung tissue. We report the case of severe respiratory failure in an immunosuppressed adult, infected with HSV-1. During hospitalization, in the Intensive Care Unit, the virus was initially found in broncho-alveolar lavage and subsequently in the cerebrospinal fluid. The patient died 18 days after admission.

Case Report

Case Description

A 44-year-old male patient was admitted in the Radiotherapy Unit, in February 2012, due to a nasopharyngeal carcinoma. Subsequently, due to the occurrence of severe respiratory failure and epileptic manifestations (seizures), the patient was admitted to the Intensive Care Unit of the same hospital. The patient required prolonged mechanical ventilation and shown persistent elevated

temperature (38-39°) and a continuous worsening of clinical symptom during the entire hospitalization. The patient did not present any significant cardiovascular or respiratory pathology in the anamnesis, but the only relevant data was the periodic manifestation of herpetic lesions from HSV-1, with a recurrence of one episode per year. During the entire stay in ICU, there was any kind of sign or typical herpetic macroscopic lesion. Blood tests showed the presence of 12,600 WBC (cells / mm^3-93% neutrophils, 4% lymphocytes, 3% monocytes), 3,610,000 RBC / mm^3, 138,000 platelets. A useful laboratory test was the monitoring of procalcitonin: lower values under the cut-off supported the hypothesis that the diagnosed bronchopulmonary infection was of viral etiology. The clinical evaluation of the patient was integrated performing 3 chest RX within a week: the first two RX showed unilateral opacities with ground glass and diffuse areas of consolidation; moreover, a modest pleural effusion was found. The third radiogram reported slight improvements.

An encephalic RMN was also performed: the images showed several areas of "edemigenic encephalitic suffering", such as the mesial cortical-subcortical region of the temporal lobes, the hippocampal area, the anterior frontal region (across the cortical region), the ethmoidal cavity and the anterior frontal-basal white matter. All these radiological findings were confirmed by TC (Figures 1-4).

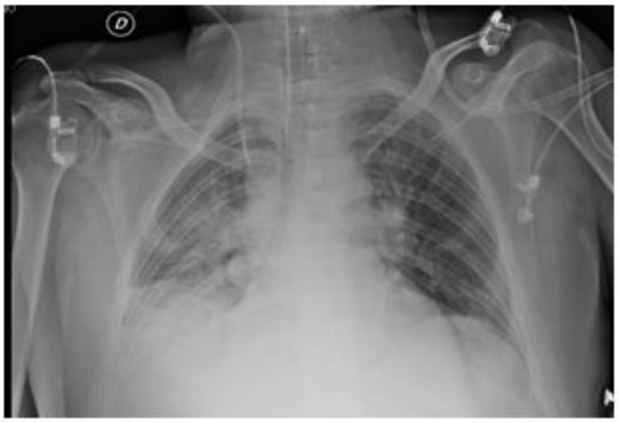

Figure 1: Chest RX shows a non-homogeneus right lung consolidation; a homolateral pleural effusion was also observed.

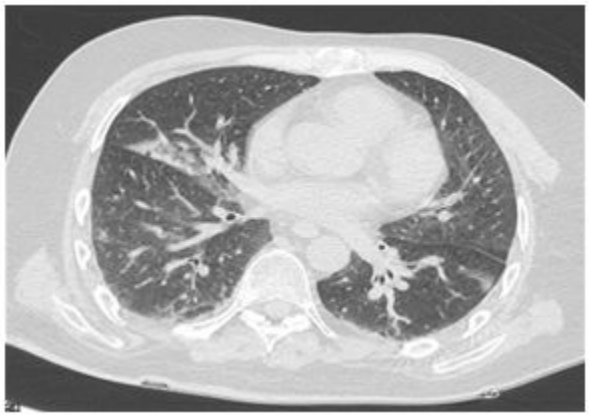

Figure 2: Ground-glass opacities and scattered areas of consolidation were found on the CT images.

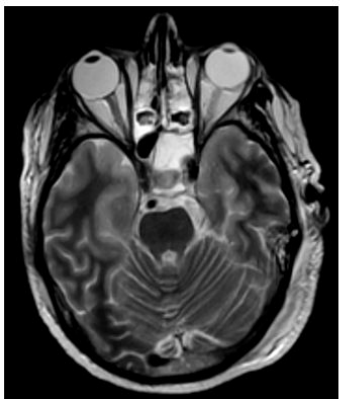

Figure 3

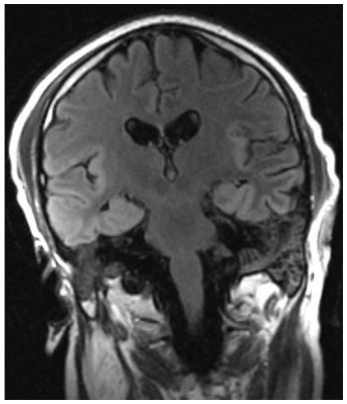

Figure 4

Figures 3-4: Axial T2- weighted image (3) and coronal FLAIR sequence (4) show high signal intensity in the cortex of both temporal lobes.

The diagnostic investigation concerning the presence of HSV-1 continued by the examination of different samples of BAL and CSF, analyzed at the Clinical Virology laboratory of the same hospital as (Figure 5) shows.

	February 21	February 23	February 28	March 6
BAL fluid[d] (Ct/copies/ml)	[b]Positive (36/<500)	Not done	[b]Positive (22/3 x 10^6)	Positive (25/1 x 10^6)
Blood (Ct/copies/ml)	Positive (>40/<500)	Positive (33/2 x 10^3)	Not done	Negative
[a]CSF (Ct/copies/ml)	Negative	[c]Positive (29/2 x 10^5)	[c]Positive (36/<500)	Negative

BAL, Bronchoalveolar lavage.

[a] Cerebral spinal fluid obtained during a surgical procedure. The real-time PCR was performed on two separate aliquots processed independently.

[b] Respiratory viruses and other herpes viruses were negative.

[c] Encephalitic viruses were negative.

[d] Ct (cycle value) cutoff threshold: <35, quantitative result; >35, qualitative result; sensitivity, 10 copies/reaction.

Figure 5: Real-time PCR results to HSV-1 according to the type of specimen and timing.

BAL and CSF were negative for bacteria, mycobacteria and fungi. The patient's general condition progressively worsened until exitus, which occurred 18 days after hospitalization.

Discussion

We reported the clinical case of a 44-year-old patient who presented, during his hospitalization, severe respiratory failure associated with epileptic manifestations. Through the analysis of several samples of BAL and CSF, our clinical investigation reported an infection of the lower airways supported by HSV-1; in addition, the virus was found in CSF samples [13-15]. The presence of viral DNA was collected in different regions and supported the hypothesis of a disseminated infection. CNS dissemination can be explained by two different theories: the first is represented by the viral distribution through the blood stream [16]. The second one could involve the reactivation of a latent infection and consider the neurotropism of herpesviridae and their transneuronal directional diffusion capacity through the synapses, interesting the sympathetic and parasympathetic nerve system [8]. On the basis of our results, in this case we consider the first hypothesis more plausible, that is the one that suggests the dissemination of the virus, from the lungs to the CNS, through the circulatory stream. By using PCR, the detection of HSV-1 in peripheral blood may be associated with either a primary infection or an exogenous or endogenous reinfection in a severely immunosuppressed patient. The clinical manifestations that can occur when HSV-1 is found in the blood are symptoms of CNS, as an alteration of mental status. As reported by Berrington, et al. [17], in 46% of patients presenting mental state alterations, the presence of HSV-1 was identified in the cephalic-rachidian liquor, after a finding in the blood stream.

In the clinical case described, the patient, positive for HSV-1, belonged to the category of subjects with a risk of exitus of 40% [5], due to the immunosuppression and severity of the underlying disease: factors that could favor an endogenous reactivation of the virus. Furthermore, the fact that the patient has been supported to prolonged mechanical ventilation increases the probability of the occurrence of respiratory infection by HSV-1, in agreement with what has been stated by several Authors: a prospective study demonstrates the presence of HSV-1 in the lower airways 64% of critically ill patients enrolled [12]. A hypothesis that we believe is plausible by comparing a study of Deback, et al. [18] is that the oral cavity represents an important reservoir of HSV-1: in this way, following a state of immunosuppression of the patient, the virus can reactivate and spread from the oropharynx to the lower airways. In immunocompromised patients subjected to mechanical ventilation, the diagnosis of HSV-1 pneumonia can be considered both as a possible triggering factor of important neurological sequelae and as an indication of worsening of the patient's clinical condition: both correlate with bad outcome. The finding of different positivity for HSV-1, in the various samples of BAL and CSF examined, allowed the start of a specific treatment by Acyclovir, despite which, the patient's condition worsened until the exitus: the reasons for the failure therapeutic may be due to resistance to acycovir [19]. The final considerations require a careful reflection on some concepts, hoping for further study, investigation and analysis.

The intensive care units apply daily numerous microbial screening protocols, especially bacterial and mycotic; viral ones also assume primary importance, but not for all pathogens belonging to this category, such as herpesviridae. HSV-1 assumes a primary role in many respiratory and neurological diseases: it mainly involves immunosuppressed subjects and in which numerous pathologies coexist; critically ill patients in intensive care units and subjected to long period mechanical ventilation. We wonder if it is not appropriate to update "our" clinical research, with the development of modern and adequate research protocols for HSV-1. Not only would the diagnostic techniques be refined for numerous pathologies that still require further investigation but would significantly increase the level of clinical-diagnostic surveillance. It would increase an early and appropriate therapy administration, reducing the rate of complications and the risk of mortality. Management of critical patients, as well as their outcome, will be affected by considerable improvement.

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