Evidence for HSV-1-induced pneumonitis in patients under standard immunosuppressive therapy for rheumatic and vasculitic autoimmune disease.

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Abstract

**Background:** Reactivation of herpes simplex virus type-1 (HSV-1) has been associated with tracheobronchitis and pneumonitis. It is a continuing matter of controversy if both conditions are relevant entities and should be treated by antiviral therapy. A body of data from critically-ill nonimmunocompromized patients under mechanical ventilation indicates that HSV-1 pneumonitis is frequent in this population and associated with poorer outcomes, but that antiviral treatment does not influence mortality. These data challenge a series of reports on the successful treatment of HSV-1 pneumonitis in patients under immunosuppressive medication or cytotoxic therapy for malignancy. Naturally, study numbers on the former group exceed those on the latter, in which scarcity of cases and individualized treatment strategies conflict the conduction of trials.

**Objectives/Study Design:** We retrospectively reviewed the charts of approximately 1080 patients with rheumatoid arthritis or vasculitis that were followed at the outpatient clinic of a University hospital in the years 2000-2007.

**Results:** A total of four cases of pulmonary infection associated with detection of HSV-1 in the lower respiratory tract were identified. Maintenance therapy with leflunomide, which inhibits HSV-1 assembly *in vitro*, was associated with a milder course of pneumonitis.

**Conclusions:** In an area of controversy, this study provides further evidence that HSV-1 causes isolated pneumonitis in immunocompromized patients that is amenable to successful treatment. For the first time, immunosuppression for rheumatic or vasculitic diseases is reported to be associated with HSV-1 pneumonitis.

**Key words:** pneumonia, herpes simplex virus, rheumatoid arthritis, Wegener’s granulomatosis, mPAN, leflunomide
1. Introduction

After infection during early life, herpes simplex virus type-1 (HSV-1) typically becomes latent residing in sensory facial nerve ganglia from where it may become reactivated during periods of immunosuppression or increased stress to the immune system. In severely immunocompromized patients and critically-ill nonimmunocompromized patients under prolonged mechanical ventilation reactivation of HSV-1 may occur and has been associated with tracheobronchitis or pneumonitis.

HSV-1 associated pneumonitis is a diagnostic challenge presenting with severe respiratory insufficiency and changes on thoracic imaging studies. However, it remains a continuing matter of controversy if these manifestations are a relevant outcome-defining pathology that must be treated.

On the one hand anecdotal reports from severely immunocompromized patients suggest the existence of HSV-1 pneumonitis as a disease-entity that can be successfully treated with antiviral agents. On the other hand studies on the subject have only been executed on nonimmunocompromized patients under mechanical ventilation. Generally, the detection rate of Herpes simplex virus on oropharyngeal swabs is high in these subjects, i.e., 22 % upon admission and 89 % within the first 10 days, as shown by a study investigating 764 patients. In a recent study, cytology/histology-proven HSV-1 pneumonitis in 42 patients under mechanical ventilation was associated with a poorer outcome, but antiviral treatment failed to be beneficial. Three additional studies of comparable size yielded similar results. Other studies seeked circumstantial evidence on various roles of HSV-1 in the intensive care setting. While a much larger interventional trial in patients under mechanical ventilation is still being awaited it remains controversial if data from these patients can also be applied to immunocompromized patients exhibiting signs of HSV-1 pneumonitis.

Here we report four cases of patients under an outpatient regimen of chronic immunosuppressive therapy for autoimmune disease who presented with respiratory deterioration that was associated with the detection of HSV-1 on initial bronchoalveolar lavage (BAL). Two cases in which no other viral, bacterial or fungal agent than HSV-1 was found and in which imaging studies were suggestive for HSV-1 pneumonitis were successfully treated with acyclovir leading to rapid clinical improvement. The remaining two cases displayed an initial co-infection with fungal or bacterial agents, and HSV-1,
required prolonged mechanical ventilation and had a fatal outcome despite adequate antiinfective
treatment that included acyclovir. In an area of controversy, the first two cases of our report provide
further evidence that in selected patients, if secured to be the sole agent, HSV-1 is a relevant pathogen
of pneumonitis that is amenable to treatment. In addition, our data demonstrate for the first time that
current standard immunosuppression for chronic rheumatic and vasculitic diseases may confer a risk
for HSV-1 pneumonitis. The remaining two cases reflect the great difficulty of dissecting the role of
HSV-1 in infections with multiple pathogens\(^6\) and illustrate that HSV-1 pneumonitis is a diagnosis of
exclusion requiring a complete microbiological workup.

2. Case study
A total of \(~80\) patients with ANCA-associated vasculitis and \(~1000\) patients with rheumatoid arthritis
were treated during the years 2000-2007 in the nephrology and rheumatology outpatient clinic at the
Medical Policlinic, LMU University of Munich. A complete retrospective chart review identified a
total of four patients that had an episode with respiratory deterioration associated with the detection of
HSV-1 in the lower respiratory tract. Upon presentation all patients had been admitted to the intensive
care unit. Short and complete summaries of the patients’ characteristics are provided in Figure 1 and
Table 1, respectively.

The four patients were aged 60-74 yrs (median 70 years). Diagnoses of the underlying systemic
autoimmune disease were rheumatoid arthritis (n=2), Wegener’s granulomatosis, and microscopic
polyangiitis with a duration of 3-10 years (average 5.7 years). All patients were on strong
immunosuppressive regimens, consisting of prednisone + oral cyclophosphamide, or of prednisone +
methotrexate + either leflunomide or the IL-1 receptor antibody, anakinra. Relevant comorbidities
were allergic asthma (Case 1), renal insufficiency (Case 3) and diabetes with diabetic nephropathy and
septic arthritis (Case 4). All patients developed respiratory deterioration in an outpatient setting and
presented 3-21 days after onset of symptoms to our emergency department. On admission all patients
showed partial respiratory insufficiency. While Cases 1 and 2 could be managed by continuous
positive airway pressure (CPAP) and oxygen-administration via facial mask through the course of the
illness, respectively, Cases 3 and 4 required intubation. Thoracic radiographies showed diffuse bilateral opacities (Cases 1-4) with additional pneumonic infiltrations in Case 4. High resolution thoracic CT (HRCT) was also performed on admission, showing isolated diffuse bilateral ground glass opacities (Cases 1, 3), pleural effusions (Case 2), or extensive bronchopneumonic infiltrates (Case 4). Diffuse bilateral opacities in both thoracic radiography and CT, as present in Case 1, are most commonly seen in isolated HSV-1 pneumonitis and are therefore shown in Figure 2. In all cases fiberoptic bronchoscopy (FOB) and BAL were performed on admission.

In Cases 1 and 2, BAL fluids demonstrated inclusion bodies in cytology and HSV-1 DNA by PCR, while PCR for cytomegalovirus (CMV) and adenovirus, microscopy for Pneumocystis jiroveci, as well as bacterial and fungal cultures were negative. Similarly, blood cultures, the serum-antigen for Aspergillus species and the urine antigen for Legionella pneumophila serogroup 1 were negative, leaving HSV-1 as the only identified pathogen. In both cases an initial empiric treatment for community-acquired pneumonia was given shortly and then discontinued while acyclovir for 14 days was started on day 2 of admission when the BAL PCR result was obtained (Figure 1, Table 1). The patients recovered completely after 7 and 11 days, respectively. Given these results and the pathologies present on imaging studies, both cases were diagnosed as isolated HSV-1 pneumonitis.

In Case 3, initial BAL culture grew Aspergillus and Klebsiella pneumoniae, a finding that was accompanied by a positive Aspergillus serum antigen. In addition, cytological assessment of BAL fluid revealed inclusion bodies and HSV-1 PCR was positive while CMV-PCR, adenovirus-PCR and examination of BAL fluid for Pneumocystis were negative. Acyclovir was added on day 2 of admission and the initial empiric antibiotic treatment was changed in the course of the illness according to resistance of pathogens. Nonetheless the patient died after 28 days (Figure 1, Table 1). In light of the pathogens present in addition to HSV-1 the diffuse ground glass pattern on CT imaging could not be attributed to HSV-1 with certainty but may be alternatively explained by Aspergillus or Klebsiella infection. A diagnosis of Aspergillus and Klebsiella pneumonia with bronchial HSV-1 replication and possible, but uncertain HSV-1 pneumonitis, was concluded.
In Case 4, both the macroscopic appearance on FOB and thoracic CT imaging suggested bronchopneumonia. Besides a positive HSV-1 and a negative CMV-PCR and Pneumocystis result, BAL revealed a positive culture for MRSA (methicillin-resistant *S. aureus*), *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. On day 2, acyclovir was added to the empiric antibiotic regimen, which was changed several times according to microbial resistance patterns. The patient died after 33 days (Figure 1, Table 1). Taken together, the presentation and the clinical course were most consistent with pneumonia due to MRSA that may have developed by haematogenous spread secondary to septic arthritis that was also present in the patient. The precise role of HSV-1 in Cases 3 and 4 remained unclear.

3. Discussion

Patients with systemic autoimmune disease have an alteration of immune responses that is due to both the action of immunosuppressive treatment as well as to the underlying condition itself. They are at increased risk for developing opportunistic infections among which respiratory tract affection is especially common and associated with potentially adverse outcomes. Clinical workup of respiratory deterioration in this setting is complicated by the fact that not only bacterial, fungal or viral infectious agents but also a pulmonary flare of the systemic disease or drug-related pulmonary toxicity must be taken into the differential diagnosis.

Indicators that raise suspicion for HSV-1 pneumonitis in immunocompromized patients upon presentation to the hospital are severe respiratory partial insufficiency combined with pathologic findings on imaging studies. Chest-x-ray usually shows segmental bilateral opacities (~95%) and pleural effusions (~50% of cases). CT may show ground-glass opacities (100%), focal consolidations (75%), and pleural effusions (88% of cases). Especially when ground-glass opacities are unaccompanied by other consolidations, they become a useful diagnostic hint in the immunocompromized, pointing to either an opportunistic infection due to Pneumocystis jiroveci, CMV, HSV-1, or other viruses. Differential diagnosis of isolated diffuse ground-glass opacities
includes (i) chronic interstitial diseases (e.g., hypersensitivity pneumonitis, acute interstitial pneumonia, sarcoidosis), (ii) acute alveolar diseases (pulmonary oedema including ARDS, pulmonary haemorrhage), or (iii) other causes (drug toxicity, bronchiolitis obliterans with organizing Pneumonia/BOOP, carcinoma) 22. In the case of pulmonary nodules on thoracic CT in the immunocompromized, larger versus smaller (< 10 mm) nodules may discriminate fungal/bacterial from viral agents, respectively 26.

Herpesvirus pneumonitis is a diagnosis of exclusion relying on clinical plausibility, positive viral testing, and imaging studies. The definition of positive viral testing is challenging. A recent study in patients under prolonged mechanical ventilation by Luyt et al. 15 employed the required combination of (i) clinical deterioration, (ii) HSV-1 detection in the lower respiratory tract by either PCR or culture, and (iii) cytological or histological evidence of inclusion bodies from either BAL fluids or biopsies to specifically define HSV-1 pneumonitis. PCR of BAL fluids is the most sensitive test, but it may be false positive due to contamination from oropharyngeal fluids 27, 15. As observed in the present study where Cases 1 and 3 had HSV-1 positive oral ulcers, oropharyngeal HSV-1 reactivation with or without mucocutaneous lesions is common in patients under immunosuppression, in critically ill patients, and even in patients with plain bacterial pneumonia 14, 6. In Luyt’s study 15, only 88 % of the patients with a positive PCR result on BAL also had positive BAL cultures. Only 43 % of the patients with a positive PCR on BAL had cytological/histological evidence of HSV-1 infection 15. Though specific, insistence on these cytological/histological criteria brings about a lack in sensitivity as illustrated by the fact that even open lung biopsies may be negative in the case of autopsy-proven HSV-1 pneumonitis 4. Serologic testing is not helpful due to high seroprevalence in the population. From a theoretical point of view, HSV-1 viraemia could be an additional specific diagnostic tool, which is, again, associated with a marked reduction in sensitivity 15. In regard to these reported reductions in sensitivity, viral cultures of BAL fluids or serum PCR for HSV-1 were not performed in the present study. However, in our view, the diagnosis of HSV-1 pneumonitis in Cases 1 and 2 appears justified in light of the clinical course and imaging studies that provided additional evidence.
In Cases 3 and 4, the precise role of HSV-1, be it none, permissive or additionally pathogenic cannot be dissected. An interesting perspective on both cases is provided by a recent report on an immunosuppressed individual with HSV-1 tracheobronchitis that suggested a potential mechanism where HSV-1 might facilitate the development of bacterial pneumonia in the outpatient setting by microaspiration. 

The viral load of BAL fluids detected by PCR correlates positively with the presence of cytology/histology-proven HSV-1 pneumonitis and negatively with outcome, but it does not seem automatically helpful in establishing a diagnosis in individual cases due to variations in sampling conditions. However, it is intriguing that Case 1 in our series who was on treatment with leflunomide showed a viral load that was 15-fold higher than the detected average while its clinical course was prolonged (21 days prior to admission to hospital) and comparatively mild. Leflunomide exhibits antiviral effects against HSV-1 by inhibiting the assembly of viral capsids but not DNA-replication at dosages used in rheumatic patients. As a purely speculative scenario, leflunomide might have led to the shedding of ill-assembled virions in Case 1. If assuming a low pathogenicity of these virions, DNA-replication might have been driven by both altered feedback-mechanisms of viral gene-regulation and a lack of host-responses. Further studies could investigate such a potential phenomenon by electron microscopy and immunolabelling studies of samples from patients on leflunomide with oral ulcers.

A possible pulmonary flare of the systemic disease or toxic methotrexate-induced pneumonitis was a differential diagnostic consideration in the patients presented herein. However, Cases 1 and 4, which were on MTX, either showed rapid resolution under acyclovir, or had a bacterial bronchopneumonia explaining the observed lesions on imaging studies alone, respectively. Cases 2 and 3, which had an autoimmune disease with pulmonary involvement showed either rapid resolution of the pneumonitis or no evidence of bleeding on FOB (a sign that would have most likely accompanied a flare of Wegener’s granulomatosis), respectively.
As outlined in the introduction, an array of anecdotal reports from severely immunocompromized subjects displaying HSV-1 as the main offending pulmonary agent has been published, where disease has been successfully treated using antivirals. This comprised patients receiving solid organ or stem cell transplantation, cytotoxic treatment for malignancy, and a report on a patient on immunosuppression for inflammatory bowel disease. The novelty of our case series lies in identifying a cluster of patients taking strong standard immunosuppressive regimens for systemic rheumatic and vasculitic disease as to be at risk for developing HSV-1 pneumonitis. So far, the following pulmonary infections, but not HSV-1 pneumonitis, have been described in this particular patient group: Pneumocystis, mycobacteria, fungi, respiratory-syncytial virus, varicella-zoster virus (with high frequency), CMV, and Epstein-Barr virus \[31, 24, 32, 33, 34, 35, 36, 37\]. When the decision for antiviral treatment in HSV-1 induced pneumonitis is made, the slowly emerging resistance of HSV-1 against acyclovir should be kept in mind \[38\].

4. Conclusion

In an area of controversy, we provide further evidence that immunocompromized patients may develop a condition that is most accurately described as HSV-1 pneumonitis. This disease can appear as an emerging non-hospital-acquired condition leading to life-threatening respiratory failure that lends itself to aggressive immunosuppression in the setting of rheumatic and vasculitic diseases.
REFERENCES


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LEGENDS

Table 1
Detailed patient data. Abbreviations used are: m= male, f= female, RA=rheumatoid arthritis, WG=Wegener's granulomatosis, mPAN=microscopic Polyangiitis, HRCT= high resolution thoracic computed tomography, bpm= breaths per minute, CrP= C-reactive protein, MRSA= Methicillin-resistant S. aureus, BAL= bronchoalveolar lavage, Ag= antigen, n.a.= not applicable, n.p.= not performed.

Figure 1
Synopsis of patient data. Abbreviations used are: MTX= methotrexate, BAL= bronchoalveolar lavage, CPAP= continuous positive airway pressure, O2-sat.= arterial blood oxygen-saturation, CT= high resolution thoracic computed tomography.

Figure 2
Imaging study from Case 1. A: Conventional chest radiographs with diffuse interstitial pattern. B: High-resolution-CT (HRCT) image of Case 1 featuring small pleural effusions and partialatelectasis of the right lower lobe in addition to distinctive ground-glass opacities.
## Figure 1

### Case 1
74 yrs (f)
**Rheumatoid arthritis, seronegative**
- Duration: 8 yrs
- Prednisone + MTX + leflunomide

**Clinical findings**
- 21 days of symptoms (cough, fever)
- Initial O2-sat: 80%
- Respiratory support: CPAP
- CT: isolated diffuse ground glass opacities
- Infectious agent
  - Only HSV-1 on BAL

**Treatment**
- Initial empiric: ceftriaxone + erythromycin (for 7 days; overlap with acyclovir 5 days)
- Start of acyclovir on day 2

**Outcome**
- Clinical recovery after 7 days

### Case 2
74 yrs (m)
**Pulmonary microscopic Polyangiitis**
- Duration: 3 yrs
- Prednisone + cyclophosphamide

**Clinical findings**
- 3 days of symptoms (bloody cough, dysphagia)
- Initial O2-sat: 86%
- Respiratory support: oxygen-mask
- CT: right-sided pleural effusion
- Infectious agent
  - Only HSV-1 on BAL

**Treatment**
- Initial empiric: moxifloxacin (2 days)
- Swapped to acyclovir monotherapy on day 2

**Outcome**
- Clinical recovery after 11 days

### Case 3
60 yrs (m)
**Wegener's granulomatosis (pulmonary + renal)**
- Duration: 2 yrs
- Prednisone + cyclophosphamide
- Comorbidity: renal insufficiency

**Clinical findings**
- 3 days of symptoms (dyspnoea, syncope)
- Initial O2-sat: 87%
- Respiratory support: intubation
- CT: isolated diffuse ground glass opacities, no granulomas suggestive of Wegener's
- Infectious agent
  - Aspergillus cultured from BAL
  - *K. pneumoniae* cultured from BAL
  - HSV-1 DNA on BAL

**Treatment**
- Initial empiric: meropenem + erythromycin + fluconazole
  - Added amphotericin B (instead of fluconazole) + acyclovir on day 2
  - Later added ciprofloxacin + tobramycin + vancomycin (instead of meropenem)

**Outcome**
- Lethal after 28 days

### Case 4
67 yrs (m)
**Rheumatoid arthritis (seropositive)**
- Duration: 10 yrs
- Prednisone + MTX + anakinra
- Comorbidity: diabetes, diabetic nephropathy, septic arthritis

**Clinical findings**
- 7 days of symptoms (dyspnoea)
- Initial O2-sat: 90%
- Respiratory support: intubation
- CT: bilateral bronchopneumonic infiltrates
- Infectious agent
  - MRSA cultured from BAL
  - *P. aeruginosa* cultured from BAL
  - *K. pneumoniae* cultured from BAL
  - HSV-1 DNA on BAL

**Treatment**
- Sequential:
  - Ceftriaxone, moxifloxacin
  - Gentamicin + tazobactam + fluconazole
  - Meropenem
  - Vancomycin, linezolid
  - Start of acyclovir on day 2

**Outcome**
- Lethal after 33 days
Additional files provided with this submission:

Additional file 1: table_1.doc, 97K
http://www.biomedcentral.com/imedia/2086763223544916/supp1.doc