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Herpes simplex virus infections in pulmonary cytology rarely represent pulmonary disease but remain a marker for mortality risk

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Introduction Herpes simplex virus (HSV) infection can be diagnosed in pulmonary cytology specimens. We sought to determine the clinical significance of this finding.

Methods Our medical records were searched for cases of HSV infection diagnosed in cytology specimens and the results compared with those in the literature.

Results In our sample, 9 patients had HSV inclusions. All patients had pulmonary disease, 8 of 9 had multi-organ system disease, and 8 of 9 had been treated with either steroids or chemotherapy. Patients were either not treated with antiviral therapy (6 of 9) or treated for oral with or without cutaneous disease only (3 of 9). Two patients died; pulmonary infection was confirmed in only 1 patient. Compared with prior series, the number of cases with 10 or fewer cells with inclusions was significantly higher (89% versus 17%, $P < 0.001$).

Conclusions Compared with prior series, most patients with HSV inclusions in pulmonary cytology specimens have fewer cells with inclusions, have oral and or cutaneous disease as well, and are not treated for pulmonary HSV. Nevertheless, this finding is associated with a risk of death, from both pulmonary infection and/or comorbid disease.

Introduction

Herpes simplex virus (HSV) infection of the respiratory tract can occur anywhere from the mouth to the alveoli,[1] and both radiographic evaluation and bronchoscopy can be of value in identifying the site of infection.[2] Patients with immunocompromised status, prolonged intubation,[3] burns,[4] and

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neoplasia[5] are at increased risk for infection, but potentially anyone,[6] including neonates and children[7-9] is at risk.[2] The presence of HSV in the lung may be associated with poorer clinical outcome.[3]

The diagnosis of HSV infection can be made on a variety of respiratory specimens, including tracheobronchial aspirates,[7] sputum, brushings, washings and bronchoalveolar lavages, and can be based on cytologic features, immunocytochemistry, molecular methods and culture.[10,11] In the cytology literature, the largest series (21 patients[12]) suggests that the cells with cytologic inclusions are relatively plentiful (mean: 131 cells), and thus would be presumably easy to identify. This has not been our experience, where cells with diagnostic inclusions are usually rare. In addition, when identified in pulmonary cytologic specimens, some older studies suggest that this most likely represents pulmonary infection, with a death rate of nearly 30%[12]; but more recent studies suggest that some of these patients may have oral disease only.[3] To further investigate this, we compared our series of HSV in pulmonary specimens with series in the literature.

Methods

The cytology records of Baptist Hospital (Miami, Fla.), Homestead Hospital (Homestead, Fla.), and the Ohio State University Wexner Medical Center (Columbus, Ohio) from January 2005 to August 2015 were reviewed for cases in which a diagnosis of HSV infection was made in a pulmonary specimen. Only cases in which the original cytologic specimens were available were included. In the cases with available material, all cases were confirmed by immunohistochemistry for HSV (HSV1 and HSV2, Cellmarque, Rockland, Calif., undiluted). Clinical information was obtained from the medical record.

Sputum, washings, and bronchoalveolar lavage specimens all had either cytospins or liquid-based preparations with or without a cell block. Brushings consisted of two alcohol-fixed slides. All specimens were stained with either hematoxylin and eosin or Papanicolaou stain.

Cytologic inclusions consisted of ground glass chromatin with or without multi-nucleation.

Statistical analysis was performed using a two-tailed Fisher's exact test and a threshold of 0.05 was considered significant.

Results

The results are summarized in Table 1. Nine patients were identified, 8 of 9 (89%) of whom were at least 60 years of age, all with pulmonary disease. Additionally 8 of 9 (89%) had multiorgan system disease, and 8 of 9 had been treated with steroids and or chemotherapy. Inclusions were identified in 2 sputums, 2 washings, and 5 bronchoalveolar lavage. In all but one case, fewer than 10 cells with cytologic inclusions were identified (Fig. 1). Multinucleated cells were not identified in 2 of the 9 cases. One patient had a positive HSV culture.

The mean number of cells with cytologic inclusions in this study was 18.8 ± 39.9, compared with 131.5 ± 220.4 in the largest prior study.[12] The number of cases with 10 or fewer cells with intranuclear inclusions in the current study was 89%, compared with only 17% in the prior study[12] ($P < 0.001$). Multinucleate cells were absent.

Three patients were treated for the clinical diagnosis of oral (with or without cutaneous) herpes and not pulmonary herpes. Two patients died within 1 week of the diagnosis, neither were treated with antiviral therapy. One of these patients had pulmonary herpes infection confirmed on autopsy and one did not have herpes infection on autopsy. A third patient was transferred to another facility for progressive deterioration based on multiorgan system failure.

Discussion

Our results are similar to and different from those of prior studies. As other studies have shown, HSV infection can be

Table 1 Clinical summary of herpes simplex virus infection.

Case no.	Age	Sex	Pulmonary Dx	Multi-organ system disease	Steroid/ chemotherapy Rx	Antiviral Rx	Specimen	No. cells
1	77	F	COPD, DAD[a]	Yes	Yes	No	BAL	4
2	78	F	CA	Yes	Yes	Yes[b]	Sputum	10
3	74	F	COPD, mucus plug	Yes	Yes	No	Washings	125
4	60	M	COPD	Yes	Yes	Topical only	Sputum	8
5	79	M	COPD	Yes	Yes	No	Washing	2
6	62	M	Bacterial pneumonia	Yes	Yes	No	BAL	5
7	37	M	Bacterial pneumonia	Yes	No	No	BAL	2
8	69	F	Bacterial pneumonia[d]	No	Yes	Yes[c]	BAL	5
9	71	M	Herpetic pneumonia[d]	Yes	Yes	No	BAL	8

Abbreviations: Dx, diagnosis; COPD, chronic obstructive pulmonary disease; DAD, diffuse alveolar damage; CHF, congestive heart failure; CA, pulmonary carcinoma; BAL, bronchoalveolar lavage.
[a]Confirmed on open lung biopsy.
[b]No fever or infiltrate, oral lesions only clinically.
[c]Clinical skin rash.
[d]Confirmed on autopsy.