Case Report
Presumed Respiratory Syncytial Virus Pneumonia in Three Immunocompromised Adults

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Abstract: Three cases of presumed respiratory syncytial virus (RSV) pneumonia in immunocompromised adults are described. Two patients had symptoms of cough, fever, and malaise, following completion of a course of combination chemotherapy for the treatment of acute lymphoblastic leukemia. The third patient, a juvenile onset diabetic, developed similar symptoms while hospitalized for severe hyperglycemia. Chest roentgenograms showed lower lobe infiltrates in both leukemic patients and a bilateral non-confluent bronchopneumonia in the diabetic patient. All patients had a marked rise in complement-fixing antibody titres to RSV, suggesting a concurrent infection with the virus. Extensive microbiological investigations failed to reveal any other etiologic agent. Nosocomial infection was considered possible. RSV is not considered a cause of pneumonia in compromised adults. Our three cases suggest that there may be a higher incidence of RSV pneumonia in compromised patients, than previously recognized. [Am J Med Sci 1983; 285(3):28-33.]

KEY INDEXING TERMS

Bronchopneumonia	*Respiratory syncytial virus*	*Immunosuppression*

Introduction

Respiratory syncytial virus (RSV) is an important pathogen of the lower respiratory tract in infants and young children,[1-4] and in persons over 50 years of age.[5-7] Epidemics of RSV infection occur during the winter and early spring of each year.[4,8-10] Primary infection confers only partial immunity to the

virus[11-13] and reinfection of adults therefore is common during epidemics.[14,15] RSV reinfection of persons in the age range of 3-50 years normally causes mild upper respiratory tract symptoms.[14-17] The mild illness may be protracted,[18] but serious lower respiratory tract involvement has never been attributed to RSV infection of otherwise healthy adults under age fifty.

We describe 3 cases of severe pneumonia that indicate RSV infection may be significant in adults with impaired immunity.

Case Reports

Patient 1

The first patient was a 34-year-old man with acute lymphoblastic leukemia, who had proven to be unresponsive to various chemotherapeutic regimens. He was readmitted to the hospital with a 24-hour history of fever and cough, five days after completing a 21-day course of Prednisone, L-Asparginase, and Vincristine. On admission, the patient had a temperature of 38.8°C, and a non-productive cough. Functional inquiry was negative. Neither hemoptysis, coryza, sore throat, pleuritic chest pain, nor shortness of breath were present. There was no cyanosis. There were some white spots and petechiae on the soft palate. Examination of the respiratory system revealed a slight dullness to percussion and diminished breath sounds at the lower left lung. Crepitations, rubs, and bronchial breathing were absent.

Laboratory data included the following values: hemoglobin 11.2 g/dl; white blood count 600/mm³ with 30% polymorphs and 70% lymphoctyes; platelets 35,000/mm³. No blast cells were seen. Chest roentgenograms, on admission, showed left lower lobe infiltrates. Repeat roentgenograms, taken during the following 48 hours, showed progressive involvement with bilateral infiltrates, first of an interstitial, and then of an alveolar pattern with consolidation in the left lower lobe. Clinically, the patient did not show any signs of deterioration, during this 48-hour period. A bilateral bronchial brush biopsy of both lower lobes and the lingular segment of the left upper lobe revealed occasional pus cells and a few columnar epithelial cells. No acid fast bacilli or tumor cells were seen. Cefamandol, Tobramycin, Septra, and Erythromycin were administered in view of a possible bacterial atypical pneumonia.

The patient gradually became afebrile, but repeat chest roentgenograms did not show any resolution of the infiltrates in the first month of illness. Indeed, an increase in consolidation in both lower lobes was noted. Later follow-up showed slow resolution bilaterally.

Sputum specimens, taken during the first 5 days of the patient's illness, yielded only normal oral flora when cultured for bacteria and fungi. Several blood cultures and urine specimens were negative. An acute phase serum specimen was obtained on the fourth day after the patient's admission, and a convalescent serum specimen 14 days later. A marked rise in complement-fixing antibody titres to Respiratory Syncytial Virus was found. The titre rose from 1:16 in the acute specimen to ≥1:512 in the convalescent serum. Antibody titres to other respiratory pathogens were not significant (Table 1).

Patient 2

The second patient was a 29-year-old man with acute lymphoblastic leukemia diagnosed five years earlier. Since that time, he underwent various regimens of combined chemotherapy, resulting in slow remissions only. He was readmitted to hospital 7 days after completing his fourth course of Cyclophosphamide, Methylprednisolone Sodium Acetate, Methotrexate, L-Asparginase, Nitrogen Mustard, Vinblastine, and Folinic Acid. Other medications included Prednisone, Allpurinol, and Septra. He presented with a 2-day history of cough, fever, and malaise.

On admission, his heart rate was 145 beats per minute, and his temperature 41°C. He appeared acutely ill cachectic, and tremulous. His mucous membranes were inflamed. A chest examination revealed decreased expansion and excursion of the left lung. Dullness to percussion and inspiratory wet crepitations were noted at the left base. Rales cleared partially, but not completely, with coughing. The cough produced a clear sputum. The right lung was clear.

The patient's hemoglobin was 13.0 g/dl, the white blood count 26,200/mm³ with 75% blast cells, 12% smudges, and 13% lymphocytes. No polymorphs were seen. The platelet count was 40,000/cu mm. A chest roentgenogram revealed a patchy left lower lobe infiltrate. Cefamandole and Tobramycin were administered intravenously for a presumed acute bacterial infection of the lung. The patient did not respond to antibiotic therapy, and a repeat chest roentgenogram, taken on the sixth day after his admission, showed extensive consolidation of the left lower lobe and a small pleural reaction at the left base. Follow-up roentgenograms, 3 weeks later, showed a diminished pleural effusion, but consolidation was still

TABLE 1

TITRES OF ANTIBODIES TO VIRUSES, FUNGI, AND PARASITES

Antigen (Serologic Test)*	Patient 1 Acute - Convalescent	Patient 2 Acute - Convalescent	Patient 3 Acute - Convalescent
Influenza A (CF)	<1:18 - <1:8	<1:8 - <1:18	<1:18 - <1:8
Influenza B (CF)	<1:8 - <1:8	<1:8 - <1:8	<1:8 - <1:8
Parainfluenza (CF)	<1:8 - <1:8	<1:8 - <1:8	<1:8 - <1:8
Respiratory Syncytial Virus (CF)	1:16 - ≥1:512	<1:8 - 1:64	<1:8 - 1:256
Adenovirus (CF)	<1:8 - <1:8	<1:8 - <1:8	<1:8 - <1:8
Mycoplasma pneumoniae (CF)	<1:8 - <1:8	<1:8 - <1:8	1:16 - 1:16
Herpes simplex (CF)	1:64 - 1:64	<1:8 - <1:8	<1:8 - <1:8
Varicella - Zoster (CF)	<1:8 - <1:8	<1:8 - <1:8	<1:8 - <1:8
Cytomegalovirus (CF)	<1:8 - <1:8	<1:8 - <1:8	1:16 - 1:16
Epstein-Barr Virus EA (IFA)	neg - neg	neg - neg	neg - neg
VCA (IFA)	1:80 - 1:80	1:80 - 1:80	1:40 - 1:40
Chlamydia (CF)	<1:8 - <1:8	<1:8 - <1:8	<1:8 - <1:8
Toxoplasma gondii (IFA)	neg - neg	1:20 - 1:20	neg - neg
Aspergillus fumigatus (ID)	neg - neg	neg - neg	neg - neg
terreus (D)	neg - neg	neg - neg	neg - neg
flavus (ID)	neg - neg	neg - neg	neg - neg
nindulans (ID)	neg - neg	neg - neg	neg - neg
niger (ID)	neg - neg	neg - neg	neg - neg
Candida albicans (ID)	neg - neg	neg - neg	neg - neg
Torulopsis glabrata (ID)	neg - neg	neg - neg	neg - neg
Cryptococcus neoformans (CF)	neg - neg	neg - neg	neg - neg
Blastomyces dermatididis (CF)	neg - neg	neg - neg	neg - neg
Histoplasma capsulatum (CF)	1:4 - 1:4	1:4 - 1:2	1:4 - 1:4
Coccidioides immitis (CF)	neg - neg	neg - neg	neg - neg

* CF = Complement fixation test, IFA = Indirect fluorescent antibody test, ID = immunodiffusion

present in the posterior basal segment of the left lower lobe.

Several sputum specimens and throat swabs yielded normal oral flora, when cultured for bacteria and fungi. Blood and urine cultures were negative. An acute serum specimen was obtained on the day of admission, and a convalescent specimen 8 days later. The titre of complement-fixing antibodies to Respiratory Syncytial Virus rose from <1:8 in the acute to 1:64 in the convalescent phase. Serological investigations showed that a wide spectrum of other micro-organisms were not contributory (Table 1).

Patient 3

The third patient was a 32-year-old woman with a 27-year history of juvenile onset diabetes mellitus. Multiple complications included diabetic retinopathy, Kimmelstiel-Wilson syndrome with chronic renal failure, hyperthyroidism, hyper-tension, neuropathy, and a history of allergies. She was insulin-dependent and on an 1100 calories diabetic diet. Her diabetes was uncontrolled. Other medications included Hydroxyzine-HCl, Allopurinol, and Hydrocortisone. She presented in the Emergency Department complaining of recurrent episodes of expressive dysphasia, and focal seizures involving the right side of her face and her right arm and leg. Her serum glucose level was extremely high (1330 mg.%). She was admitted to hospital for treatment of her hyper-glycemia and further investigation.

On the third day post-admission, the patient developed a sore throat, coryza, and an irritating non-productive cough. She was afebrile. Her chest was clear, and chest roentgenograms were normal. There was little change in her condition over the following 5 days. On the ninth day of her hospitalization, the patient became febrile with a temperature of 38°C. Her non-productive cough increased, and she complained of chest pain.

Examination of her chest revealed dullness to percussion, which extended from both bases to the tip of the scapula, and bronchial breathing at the right lower lung. Scattered rhonchi and bilateral basal crepitations were noted. Chest roentgenograms showed a bilateral non-confluent bronchopneumonia. Both lower and the right middle lobes were affected. Small effusions were seen bilaterally and within the major and minor fissures. The patient's hemoglobin level was 11.0 g/dl, and the hematocrit 33%. Her white blood count was 12,900/mm^3 with 75% polymorphs, 1% basophils, 14% lymphocytes, and 10% monocytes. The patient's pO$_2$ had fallen to 44 mmHg from an admission value of 125 mmHg. A diagnosis of hypoxia secondary to pneumonia was made. Tobramycin and Cefazolin were administered intravenously, and oxygen therapy was initiated. The patient made a gradual recovery over the next 6 days. At this time, she was afebrile and breathing more easily. Her pO$_2$ increased to 93 mmHg, and oxygen therapy was discontinued. Her chest symptoms improved markedly. Only a few coarse crepitations and occasional diffuse rhonchi were heard in the basal regions. Follow-up roentgenograms, taken approximately 1 month after onset of the patient's illness, showed a marked reduction in the density of the pneumonic consolidation throughout both lung fields, and a decrease in the bilateral pleural effusions. A diffuse mottled infiltration persisted throughout both the mid and lower lung fields.

Culture of throat swabs and sputum specimens taken during the acute stages of the patient's illness did not yield any pathogenic bacteria or fungi. Several urine and blood cultures yielded no growth. Acute and convalescent serum specimens were obtained ten days apart. The titre of complement-fixing antibodies to Respiratory Syncytial Virus rose from <1:8 in the acute to 1:256 in the convalescent specimen. Serological examination for other microorganisms was negative (Table 1).

Discussion

Respiratory syncytial virus is not recognized as an important pathogen in compromised hosts. One report has associated this virus with lower respiratory tract disease in an adolescent with nephrotic syndrome,[19] but the significance of RSV infection in compromised patients is not known. We present 3 immunocompromised adult patients with roentgenographically confirmed pneumonia and serologically proven concomitant RSV infections.

Unfortunately, RSV was only implicated in our patients' illnesses after the convalescent serum results had been obtained, and no attempt to isolate the virus could be made at that late stage. Identification of RSV as the causative agent must therefore remain presumptive. However, the possible involvement of pathogens, commonly associated with pulmonary infections in immunocompromised patients,[20,21] was eliminated by the extensive serologic and microbiologic investigations which we reported. Infection with RSV occurs in all age groups during annual epidemics,[14,15] and we suggest that infection with RSV may be a cause of bronchopneumonia in immunocompromised patients.

The peak period of RSV-associated lower respiratory tract infection in otherwise healthy patients is during the second to sixth months of life, and is confined almost entirely to the first 2 years of life.[1,9] The immunologic factors that protect older children and adults against lower respiratory tract disease following RSV infection are not well understood. Serum neutralizing antibodies lessen the severity of pneumonia caused by RSV, but they do not prevent the occurrence of the disease.[22] Interferon does not appear to play a major role in protection from RSV disease[23] and the contribution of specific secretory IgA antibody is, as yet, undefined.[24] A specific cell-mediated immune response (CMI) develops following natural infection with RSV,[25,26] but its role in the pathogenesis of RSV infection is controversial. Scott and co-workers[26] found that RSV infection resulted in an exaggerated CMI response in children less than six months of age, and proposed that cell-mediated hypersensitivity reactions might contribute to the increased sensitivity to the virus observed within this age group. In contrast, other investigators have demonstrated RSV specific CMI reactivity in healthy adults and older children, but not in infants or samples of cord blood.[27] The latter observation would suggest that a lack of effective CMI might contribute to the severity of RSV disease in younger patients. The major immune defect in our patients was probably a depression of CMI.

The underlying diseases of all three patients required that they be treated with a variety of cytotoxic drugs and/or corticosteroids, whose suppressive effects on CMI are widely recognized.[28]

RSV is a major cause of nosocomial illness on neonatal wards,[29,30] and strict infection control procedures are necessary to prevent spread of the virus amongst patients and hospital staff who may serve as vectors for transfer of the virus.[31] It is noteworthy that our two leukemic patients presented with respiratory symptoms within 5 days of discharge from hospital following chemotherapy, and the diabetic patient developed symptoms on the third day post-admission. Both leukemic patients were occupants of the same ward, and RSV infection was sero-diagnosed in 2 additional patients with mild upper respiratory tract illness on the ward. The incubation period for RSV infection is 3-5 days,[32] and nosocomial infection is therefore a distinct possibility in all 3 of our patients. Control measures to prevent nosocomial RSV infections may be warranted for the management of compromised patients. However, the immunological response to RSV infection is not understood sufficiently at present to provide effective preventative measures or specific treatment for compromised patients.
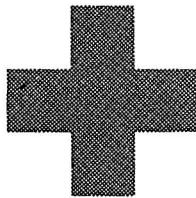
Acknowledgment

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