Human Coronavirus OC43 Pneumonia in a Pediatric Cancer Patient With Down Syndrome and Acute Lymphoblastic Leukemia

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Summary: In this report, we describe a case of pneumonia due to an infection with human coronaviruses (HCoVs)-OC43 in a pediatric leukemia patient with Down syndrome and febrile neutropenia. Not only the recently discovered HCoVs NL63 or HKU1 but also the prototype strains HCoV-OC43 and HCoV-229E have to be considered as respiratory pathogens in immunocompromised pediatric cancer patients. The routine utilization of polymerase chain reaction-based diagnostic tools would certainly elucidate the etiology of a relevant proportion of ''pneumonias of unknown origin'' in immunocompromised pediatric patients and would contribute to a better understanding of the role of HCoVs in this setting.

Key Words: pediatric cancer, febrile neutropenia, pneumonia, human coronavirus

(*J Pediatr Hematol Oncol* 2007;29:432–434)

Since the SARS outbreak in 2002/2003 and the identification of the SARS coronavirus,[1] several human coronaviruses (HCoVs) like NL63[2,3] and HKU1[4] were newly identified. Most of them have been described as respiratory pathogens with worldwide distribution. Furthermore, long known coronaviruses as HCoV-OC43 and HCoV-229E may also cause nearly identical symptoms like the newly detected viruses, thus leading to the need for a more sophisticated differential diagnosis. Hitherto, HCoV-OC43 infection has not been described in pediatric patients with Down syndrome and information on HCoV-OC43 infection in pediatric cancer patients is rather limited. We report the first case of a pneumonia caused by HCoV-OC43 in a patient with acute lymphoblastic leukemia (ALL) and Down syndrome.

Received for publication October 5, 2006; accepted March 27, 2007.

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Supported by grants from the Else Kröner-Fresenius Stiftung (Grant number A 01/05//F 00) and the BONFOR program of the Medical Faculty of the University of Bonn (Grant number O-151.0028).

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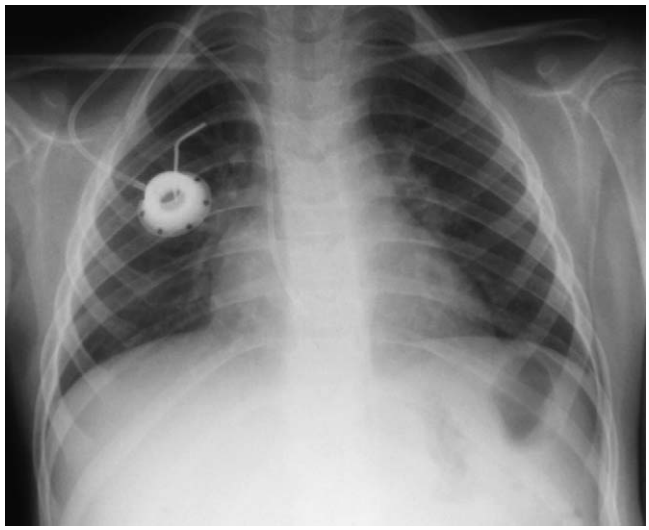
CASE REPORT

The patient was a 5-year-old boy with Down syndrome who had been admitted to our hospital with ALL in September 2005. The induction chemotherapy according to the ALL BFM 2000 protocol of the German Society of Pediatric Oncology and Hematology[5] was complicated by life-threatening bacterial infections. Thus, the typical time schedule had to be postponed and the patient reached the intensive consolidation part (protocol II median risk group) in March 2006. After a short outpatient history of cough, parallel with a respiratory tract infection in his older sibling, the patient was admitted to the hospital on April 17 with high-grade fever (39.8°C) in a reduced general condition but without dyspnea (26/min; capillary pCO_2 39 mm Hg; oxygen saturation 96% on pulse oximetry without supplemental oxygen). Auscultation yielded bronchitic inspiratory rales without wheezing or retractions and no signs of pleural effusion. His white blood cell count revealed a neutropenia with 1.2×10^9 leukocytes/L (granulocytes 0.27×10^9/L), hemoglobin 9.9 g/dL, and thrombocytes 33×10^9/L. Serum C-reactive protein concentration and interleukin-8 were elevated with 128 mg/L (normal: < 3) and 512 pg/mL (< 50), respectively. Because of his reduced general condition, which was interpreted as a clinical sign of an impending sepsis, he received piperacillin-tazobactam and tobramycin through his port catheter without delay after blood cultures had been drawn from his port catheter.

Dexamethasone, which represented a regular component of his chemotherapy, was tapered in a few days. A red blood cell transfusion was administered. Chest x-ray examination confirmed the diagnosis of a central pneumonia with both sided perihilar infiltrates (Picture 1). While the fever did not resolve after 72 hours and the initial blood and urine cultures remained sterile, fosfomycin was added as a third antibiotic[6] after 72 hours. His condition improved in parallel to an increase in white blood cell counts to 2.7×10^9 leukocytes/L after a period of neutropenia of 6 days, when the intravenous antibiotic treatment was stopped. He was released from hospital on the next day with clarithromycin as oral medication for additional 7 days. One month later, a chest radiograph showed normal findings.

VIROLOGIC RESULTS

Investigated material was nasopharyngeal aspirate[7] diluted in physiologic sodium chloride. Viral RNA and DNA were extracted as described earlier[8] and real-time polymerase chain reaction (RT-PCR) for coronaviruses,[9] human metapneumovirus,[10] respiratory syncytial virus, influenza viruses A and B, and bocavirus[11] were



PICTURE 1. Central pneumonic infiltrates in a by with ALL, febrile neutropenia, and HCoV-OC43 infection.

performed. Except the RT-PCR for coronaviruses, all PCR and RT-PCR reactions were negative. Direct sequencing (from both sides) of the coronavirus RT-PCR amplificate revealed HCoV-OC43 RNA in the patient's specimen. The sequences were aligned to published HCoV-OC43 sequences (Fig. 1),[12] accession numbers of reference strains are listed in the figure. No nucleotide exchanges were observed in the analyzed region.

DISCUSSION

This is the first report of a pediatric ALL patient with Down syndrome, who experienced an episode of febrile neutropenia and pneumonia related to an infection

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                    15201                                                15250
AY391777  (15201) GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG
AY585228  (15200) GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG
AY585229  (15200) GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG
AY903459  (15201) GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG
AY903460  (15201) GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG
patient           GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG
Consensus (15201) GTTAGTAGTTTGGTATTAGCCCGAAAACATGAGACATGTTGTTCGCAAAG

                    15251                                                15300
AY391777  (15251) CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA
AY585228  (15250) CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA
AY585229  (15250) CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA
AY903459  (15251) CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA
AY903460  (15251) CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA
patient           CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA
Consensus (15251) CGATAGGTTTTATCGACTTGCGAATGAATGCGCACAAGTTTTGAGTGAAA

                    15301                          15336
AY391777  (15301) TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
AY585228  (15300) TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
AY585229  (15300) TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
AY903459  (15301) TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
AY903460  (15301) TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
patient           TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
Consensus (15301) TTGTTATGTGTGGTGGCTGTTATTATGTTAAGCCTG
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FIGURE 1. Alignment of the OC43 sequence revealed from the patients material with known OC43 strains. Sequencing was performed from both sides, no nucleotide exchanges were observed in the sequenced region. The alignment was performed with the Vector NTI package (Invitrogen, Karlsruhe, Germany).

with HCoV-OC43. Not only his malignancy and its intensive immunosuppressive treatment (including high dose dexamethasone) but also Down syndrome[13] may have contributed to the lower respiratory tract infection this patient.

The 2 groups of HCoVs represented by the prototype strains HCoV-229E and HCoV-OC43 are mostly known as viruses responsible for common cold syndrome. HCoVs are difficult to detect and epidemiologic data are rare. Vabret et al[14] detected HCoV-OC43 in samples obtained from 30 (6%) of 501 patients out of all age groups in a prospective surveillance study from France. The following clinical symptoms were noted: fever (in 60% of patients), general symptoms (in 30%), digestive problems (in 57%), rhinitis (in 37%), pharyngitis (in 30%), laryngitis (in 3%), otitis (in 13%), bronchitis (in 17%), bronchiolitis (in 10%), and pneumonia (in 7%).

Chiu et al[15] investigated hospitalized children with fever and acute respiratory symptoms in Hong Kong during the period from August 2001 to August 2002. Coronavirus infections were detected in 26 (4.4%) of 587 children; 15 (2.6%) were positive for HCoV-NL63, 9 (1.5%) were positive for HCoV-OC43, and 2 (0.3%) were positive for HCoV-229E. HCoV-NL63 infections were noted in the spring and summer months of 2002, whereas HCoV-OC43 infection mainly occurred in the fall and winter months of 2001. Legg et al[16] from Southampton, UK, detected coronaviruses (serotypes OC43 and 229E) in 9% of 88 infants who were prospectively monitored for community acquired illness through their first winter.

Arden and coworkers[17] reported the case of a 3-month-old patient with Down syndrome admitted to the hospital with coryza, cough, respiratory distress, vomiting, and wheeze who eventually was found to have a HCoV-NL63 infection. The same paper described a 62-year-old patient with chronic lymphatic leukemia and neutropenia, who acquired HCoV-NL63 infection after bone marrow transplantation. Both patients experienced a favorable outcome, as did our patient. Both coronaviruses NL63 and OC43 seem to induce similar respiratory symptoms, although they form 2 different coronavirus genotypes. The relative risk of contracting HCoV-infection in immunocompromised patients was twice that of immunocompetent patients.[18] Thus, it has been concluded that the investigation of HCoV should be considered in lower respiratory tract secretions from transplant recipients with bronchiolitis and pneumonia (Ref. 18, 6779).

In immunocompromised children, the period of contagiosity may be longer than 1 week. It has to be determined, whether the patient is still contagious after full clinical recovery, when HCoV-OC43 is still detected with highly sensitive RT-PCR methods. Experiences with other viral respiratory pathogens suggest that viral loads may be higher and viral shedding may be prolonged in immunocompromised individuals (Ref. 7, 6301, Ref. 19, 106). Health care staff members, parents, and visitors may act as symptomatic or asymptomatic vectors for the nosocomial transmission of HCoV.[20] As nosocomial

transmission has to be prevented in particular in cancer patients, rapid detection of the virus, and also isolating or cohorting of HCoV-OC43 cases seem desirable.

REFERENCES

1. Drosten C, Gunther S, Preiser W, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med*. 2003;348:1967–1976.
2. van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. *Nat Med*. 2004;10:368–373.
3. Fouchier RA, Rimmelzwaan GF, Kuiken T, et al. Newer respiratory virus infections: human metapneumovirus, avian influenza virus, and human coronaviruses. *Curr Opin Infect Dis*. 2005;18:141–146.
4. Woo PC, Lau SK, Tsoi HW, et al. Clinical and molecular epidemiological features of coronavirus HKU1-associated community-acquired pneumonia. *J Infect Dis*. 2005;192:1898–1907.
5. Grigull L, Beier R, Schrauder A, et al. Invasive fungal infections are responsible for one-fifth of the infectious deaths in children with ALL. *Mycoses*. 2003;46:441–446.
6. Simon A, Bode U, Beutel K. Diagnosis and treatment of catheter-related infections in paediatric oncology: an update. *Clin Microbiol Infect*. 2006;12:606–620.
7. Wilkesmann A, Schildgen O, Eis-Hubinger AM, et al. Human metapneumovirus infections cause similar symptoms and clinical severity as respiratory syncytial virus infections. *Eur J Pediatr*. 2006; 165:467–475.
8. Simon A, Groneck P, Kupfer B, et al. Detection of bocavirus DNA in nasopharyngeal aspirates of a child with bronchiolitis. *J Infect*. 2007;54:e125–e127.
9. Moes E, Vijgen L, Keyaerts E, et al. A novel pancoronavirus RT-PCR assay: frequent detection of human coronavirus NL63 in children hospitalized with respiratory tract infections in Belgium. *BMC Infect Dis*. 2005;5:6.
10. Schildgen O, Geikowski T, Glatzel T, et al. New variant of the human metapneumovirus (HMPV) associated with an acute and severe exacerbation of asthma bronchiale. *J Clin Virol*. 2004;31: 283–288.
11. Allander T, Tammi MT, Eriksson M, et al. Cloning of a human parvovirus by molecular screening of respiratory tract samples. *Proc Natl Acad Sci USA*. 2005;102:12891–12896.
12. Vijgen L, Keyaerts E, Lemey P, et al. Evolutionary history of the closely related group 2 coronaviruses: porcine hemagglutinating encephalomyelitis virus, bovine coronavirus, and human coronavirus OC43. *J Virol*. 2006;80:7270–7274.
13. de Hingh YC, van der Vossen PW, Gemen EF, et al. Intrinsic abnormalities of lymphocyte counts in children with down syndrome. *J Pediatr*. 2005;147:744–747.
14. Vabret A, Mourez T, Gouarin S, et al. An outbreak of coronavirus OC43 respiratory infection in Normandy, France. *Clin Infect Dis*. 2003;36:985–989.
15. Chiu SS, Chan KH, Chu KW, et al. Human coronavirus NL63 infection and other coronavirus infections in children hospitalized with acute respiratory disease in Hong Kong, China. *Clin Infect Dis*. 2005;40:1721–1729.
16. Legg JP, Warner JA, Johnston SL, et al. Frequency of detection of picornaviruses and seven other respiratory pathogens in infants. *Pediatr Infect Dis J*. 2005;24:611–616.
17. Arden KE, Nissen MD, Sloots TP, et al. New human coronavirus, HCoV-NL63, associated with severe lower respiratory tract disease in Australia. *J Med Virol*. 2005;75:455–462.
18. Gerna G, Campanini G, Rovida F, et al. Genetic variability of human coronavirus OC43-, 229E-, and NL63-like strains and their association with lower respiratory tract infections of hospitalized infants and immunocompromised patients. *J Med Virol*. 2006;78: 938–949.
19. Hicks KL, Chemaly RF, Kontoyiannis DP. Common community respiratory viruses in patients with cancer: more than just "common colds". *Cancer*. 2003;97:2576–2587.
20. Gagneur A, Sizun J, Vallet S, et al. Coronavirus-related nosocomial viral respiratory infections in a neonatal and paediatric intensive care unit: a prospective study. *J Hosp Infect*. 2002;51: 59–64.

ERRATUM

Mehran Hiradfar, Nona Zabolinejadm, Abdolla Banihashem, Abdol-Mohammad Kajbafzadeh. Renal Splenic Heterotopia With Extramedullary Hematopoiesis in a Thalassemic Patient, Simulating Renal Neoplasm: A Case Report. *J Pediatr Hematol Oncol*. 2007;29:195–197.

In the article on page 195, the second author's name was misspelled. It should be Nona Zabolinejad, MD. The Journal apologizes for this error.