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CONCISE ARTICLE

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Community-acquired adenovirus pneumonia in a patient with chronic lymphatic leukaemia

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Abstract Described here is a severe case of community-acquired adenovirus pneumonia that occurred in a previously healthy 54-year-old male who was later determined to have stage A chronic lymphatic leukemia. The clinical presentation was consistent with that of atypical pneumonia. Testing with PCR revealed adenovirus in a bronchoalveolar lavage sample, while all other tests to determine a bacterial or virological etiology were negative. Further examination of the patient revealed the previously undiagnosed chronic lymphatic leukemia. Following treatment with human immunoglobulin and oxygen therapy with continuous positive airway pressure support the patient recovered from the pneumonia completely.

Introduction

Adenoviruses are ubiquitous and can cause a variety of human ailments including upper and lower respiratory tract diseases, conjunctivitis, and gastroenteritis. These infections are usually mild and self-limited and are mostly seen in young children and in adults living close together, such as military recruits. Only rarely does severe infection develop in subjects presumed to be healthy [1, 2]. However, the potential of adenoviral infection to disseminate and cause severe illness in immunocompromised patients, such as those undergoing bone marrow or solid organ transplantation [3, 4] and those with malignant neoplasms [5] and HIV infection [6], has been well described. The mortality in such patient populations is reported to be high. We describe here a case of community-acquired pneumonia caused by adenovirus in a previously healthy patient who was later shown to have stage A chronic lymphatic leukemia (CLL).

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Case report

A 54-year-old previously healthy non-smoking male was admitted to a local hospital with a short history of fever and upper respiratory tract symptoms, non-productive cough and shortness of breath that was not relieved by a 3-day course of oral amoxicillin. Physical examination showed moderate dyspnea, coughing, and a temperature of 38.8°C; conjunctivitis, pharyngitis, gastroenteritis and rash were not observed. Inspiratory crackles were noted on the left upper thorax. Cardiovascular and abdominal findings were unremarkable. Routine laboratory tests revealed a hemoglobin count of 7.5 mmol/l, leukocytosis of 35×109/l, thrombocyte count of 114×109/l, C-reactive protein 269 mg/l (normal, <10 mg/l), bilirubin 12 µmol/l (normal, <21 µmol/l), and S-aspartate aminotransferase 132 U/l (normal, 10–50 U/l). Chest radiograph revealed an infiltrate on the upper left side, and therapy with intravenous penicillin was initiated since pneumococcal pneumonia in Denmark remains sensitive to this agent. Blood cultures were negative, and attempts to obtain a sputum sample were unsuccessful.

Over the following 4 days the patient's condition deteriorated with increasing fever, severe dyspnea, jaundice and mental alterations. Arterial blood gas analysis in ambient air showed a PO_2 of 6.4 kPa, a PCO_2 of 4.0 kPa, and a pH of 7.49. The patient was transferred to our hospital because of worsening signs on chest radiographs and increasing oxygen requirements. Laboratory tests performed at admission to our hospital revealed increased leukocytosis at 62.4×109/l (95% lymphocytes), C-reactive protein 171 mg/l, bilirubin 96 µmol/l, S-aspartate aminotransferase 132 U/l, lactate dehydrogenase 867 U/l (normal, <450 U/l), and alkaline phosphatase 629 U/l (normal, 70–275 U/l). Evaluation of jaundice revealed a negative Coombs test and no indication of hemolysis. A posteroanterior chest radiograph showed consolidation of the lingual and left upper lobes as well as right-sided perihilar infiltrates (Fig. 1). Respiratory support was provided for 6 days via a continuous positive airway pressure system on a face mask.

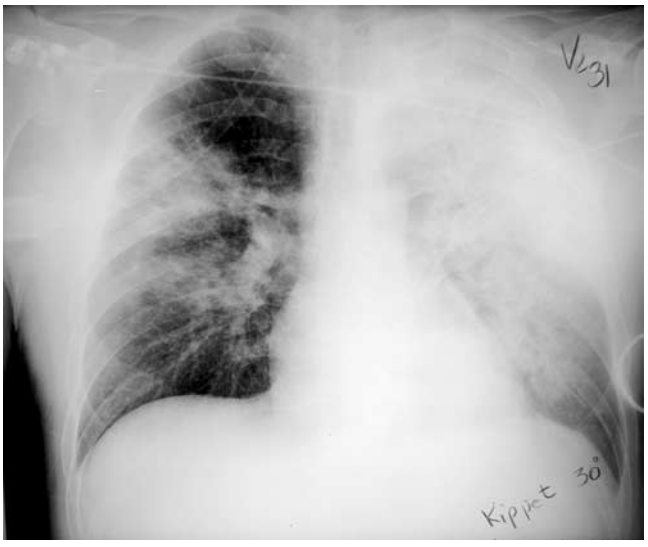

Fig. 1 Posteroanterior chest radiograph obtained after 10 days of respiratory symptoms

Atypical pneumonia was suspected and empiric antibacterial therapy with erythromycin and rifampicin (later ciprofloxacin) was administered for 3 weeks. Hypogammaglobulinemia was diagnosed after an IgG count of 4.0 g/l (normal, 6.1–14.9 g/l) was obtained, and 20 g of human immunoglobulin was administered intravenously. The patient recovered slowly and was discharged without respiratory symptoms.

Diagnostic evaluation included bacterial cultures of blood and urine, all of which were negative. Urine was also negative for *Legionella pneumophila* antigen. Bronchoscopy was performed after admission to our hospital, and bronchoalveolar lavage (BAL) fluid was cultured for bacteria, fungi and mycobacteria with negative results. Polymerase chain reaction performed on BAL fluid was positive for adenovirus but negative for influenza virus, parainfluenza virus, coronavirus, respiratory syncytial virus, pneumoocystis, and *Legionella*, *Mycoplasma*, and *Chlamydia* spp. Serological tests for *Legionella*, *Mycoplasma* and *Chlamydia* spp. performed at admission and at 2 and 8 weeks after the onset of symptoms were also negative (all <1:16). Serum tests for HIV antibody, antinuclear antibody, and antibodies to hepatitis B and C viruses were negative.

Due to the clinical finding of an enlarged lymph node on the left side of the neck and marked lymphocytosis in peripheral blood, a bone marrow examination was performed. The test revealed CLL at stage A.

Discussion

The case reported here of a previously healthy patient with pneumonia from whom adenovirus was the only pathogen demonstrated represents a very rare event, even in patients with an established immunosuppressive disorder. A previous review of autopsy results from a large series of immunocompromised patients identified just 0.5% of cases with disseminated adenovirus infection [7]. From a prospective study of respiratory virus infections in patients with hematologic malignancies, adenoviral disease was confirmed in 6% of cases, but the complete absence of pneumonia in these patients [5] suggests the complication seen in our patient is rare. Even in cases of severe immunosuppression, such as that due to bone marrow transplantation, adenovirus pneumonia occurs rarely [3].

In the case reported here, further diagnostic evaluations revealed the patient had previously undiagnosed stage A CLL. However, it is difficult to assess the influence of this comorbidity on the course of the adenoviral infection. In the literature, only two other reports have identified patients with CLL and adenoviral pneumonia, and both patients had a fatal outcome [7, 8]. Nevertheless, it is clear from those two reports, that the patients were far more immunocompromised than ours, with one patient having received multiple courses of chemotherapy and the other having cytopenia at the time of diagnosis [7, 8]. Patients with CLL frequently have low levels of immunoglobulin, as did our patient, and most of the infectious complications they experience are caused by bacteria. Severe viral infections, with the exception of reactivated herpes zoster, are rare in this patient population. Nevertheless, the case presented here reflects the possibility that an unusual viral etiology can play a role in lower respiratory tract infections.

In light of the recent emergence of the SARS-coronavirus syndrome it is particularly relevant to include virological examinations in the diagnostic work-up of patients with severe pneumonia of unknown etiology. Our patient was admitted during the annual influenza epidemic, but we did not detect coronavirus or any other respiratory viruses (except for adenovirus) by PCR performed on BAL fluid, nor did we culture any bacteria, fungi or mycobacteria from blood or BAL. The application of PCR for the detection of respiratory viruses in adults with pneumonia is the technique of choice [9], and the increased use of PCR may lead to more frequent detection of a viral etiology in cases of atypical pneumonia owing to the method's better sensitivity.

Frequently, severe adenovirus infection in immunocompromised patients involves several organs due to its role in several forms of disease, i.e. hepatitis, gastroenteritis, hemorrhagic cystitis and possibly encephalitis. Our patient had mild-to-moderate signs of hepatic involvement with jaundice and increased liver enzymes as well as a brief period of cerebral symptoms. The manifestations in both organs regressed spontaneously. At presentation and for several days thereafter the patient had significantly elevated levels of C-reactive protein, which suggested a bacterial etiology. However, among the respiratory viruses, adenovirus in particular is known to induce a strong C-reactive protein response [10]; thus, we accept adenovirus infection as the cause of the acute-phase reactant response seen in our patient.

Although other types of viral pneumonia are associated with diffuse infiltrates on chest radiology, adenoviral pneumonia is frequently reported to present with focal infiltrates [11] and, in practice, cannot be distinguished from atypical bacterial pneumonia [12]. In the present case the

clinical presentation was suggestive of atypical pneumonia, and treatment with macrolides and a fluoroquinolone was administered for 3 weeks on suspicion of legionellosis. However, examinations of BAL by culture and PCR did not detect any *Legionella* species, and repeated serological examinations did not show any rise in antibody titre against legionella antigens; thus, we do not believe this pathogen was associated with our patient's symptoms. Respiratory support was successfully provided via a continuous positive airway pressure system, which has previously been reported to help reduce the risk of morbidity and mortality associated with mechanical ventilation in patients with viral pneumonia [13, 14].

Despite promising in vitro findings, no antiviral medication has yet been shown to change the course of adenoviral disease. Ribavirin and cidofovir have been tried in a limited number of cases with unclear results [3, 15, 16]. At the time we were notified that adenovirus had been detected in our patient's BAL, the patient was improving clinically, so we decided not to initiate antiviral therapy. Since a low level of IgG was detected (secondary to CLL) the patient was given human immunoglobulin, which in itself may have antiviral efficacy. Initiation of corticosteroid therapy for the CLL was postponed until regression of the pneumonia was observed, since steroid therapy may worsen adenoviral pneumonia [11, 17].

In conclusion, newer and more sensitive diagnostic methods may reveal more cases of viral pneumonia in mildly immunocompromised hosts. The case presented here demonstrates it may be appropriate to consider the possibility of a comorbid immunosuppressive condition in cases of adenoviral pneumonia.

References

1. Komshian SV, Chandrasekar PH, Levine DP (1987) Adenovirus pneumonia in healthy adults. Heart and Lung 16:146–150
2. de Roux A, Marcos MA, Garcia E, Mensa J, Ewig S, Lode H, Torres A (2004) Viral community-acquired pneumonia in nonimmunocompromised adults. Chest 125:1343–1351
3. La Rosa AM, Champlin RE, Mirza N, Gajewski J, Giralt S, Rolston KV, Raad I, Jacobson K, Kontoyiannis D, Elting L, Whimbey E (2001) Adenovirus infections in adult recipients of blood and marrow transplants. Clin Infect Dis 32:871–876
4. Raboni SM, Nogueira MB, Tsuchiya LRV, Takahashi GA, Pereira LA, Pasquini R, Siqueira MM (2003) Respiratory tract viral infections in bone marrow transplant patients. Transplantation 76:142–146
5. Martino R, Ramila E, Rabella N, Munoz JM, Peyret M, Portos JM, Laborda R, Sirra J (2003) Respiratory virus infections in adults with hematologic malignancies: a prospective study. Clin Infect Dis 36:1–8
6. King JC (1997) Community respiratory viruses in individuals with human immunodeficiency virus infection. Am J Med 102(3A):19–24
7. Pham TTN, Burchette JL, Hale LP (2003) Fatal disseminated adenovirus infections in immunocompromised patients. Am J Clin Pathol 120:575–583
8. Ljungman P, Ehrnst A, Björkstrand B, Hellström E, Ingelman-Sundberg H, Juliusson G, Lönnqvist B (1990) Lethal disseminated adenovirus type 1 infection in a patient with chronic lymphocytic leukemia. Scand J Infect Dis 22:601–605
9. van Elden LJR, van Kraaij MGJ, Nijhuis M, Hendriksen KAW, Dekker AW, Rozenbeg-Arska M, van Loon AM (2002) Polymerase chain reaction is more sensitive than viral culture and antigen testing for the detection of respiratory viruses in adults with hematological cancer and pneumonia. Clin Infect Dis 34:177–183
10. Kawasaki Y, Hosoya M, Katayose M, Suzuki H (2002) Correlation between serum interleukin-6 and C-reactive protein concentrations in patients with adenoviral respiratory infections. Pediatr Infect Dis J 21:370–374
11. Klinger JR, Sanchez MP, Curtin LA, Durkin M, Matyas B (1998) Multiple cases of life-threatening adenovirus pneumonia in a mental health care center. Am J Respir Crit Care Med 157:645–649
12. Motallebi M, Mukunda BN, Ravakhah K (2003) Adenoviral bronchopneumonia in an immunocompetent adult: computed tomography and pathologic correlations. Am J Med Sci 325:285–287
13. Pearson RD, Hall WJ, Menegus MA, Douglas RG (1980) Diffuse pneumonitis due to adenovirus type 21 in a civilian. Chest 78:107–109
14. Taylor GJ, Brenner W, Summer WR (1976) Severe viral pneumonia in young adults: therapy with continuous positive airway pressure. Chest 69:722–728
15. Leruez-Ville M, Minard V, Lacaille F, Buzyn A, Abachin E, Blanche S, Freymuth F, Rouzioux C (2004) Real-time blood plasma polymerase chain reaction for management of disseminated adenovirus infection. Clin Infect Dis 38:45–52
16. Lankester AC, Heemskerk B, Claas ECJ, Schilham MW, Beersma MFC, Bredius RGM, van Tol MJD, Kroes ACM (2004) Effect of ribavirin on the plasma viral DNA load in patients with disseminating adenovirus infection. Clin Infect Dis 38:1521–1525
17. Dudding BA, Wagner SC, Zeller JA, Gmelich JT, French GR, Top FH (1972) Fatal pneumonia associated with adenovirus type 7 in three military trainees. N Engl J Med 286:1289–1292