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Official publication of the American College of Chest Physicians



Occupational Asthma Due to Colistin in a Pharmaceutical Worker

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Chest 2010;137:1200-1202
DOI 10.1378/chest.09-1881

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ISSN:0012-3692



15. Drevelengas A, Kalaitzoglou I, Petridis A. Pneumorrhachis associated with spontaneous pneumomediastinum. *Eur J Radiol.* 1994;18(2):122-123.
16. Drolet S, Gagné JP, Langis P. Spontaneous pneumorrhachis associated with pneumomediastinum in a patient with diabetic ketoacidosis: an exceptional manifestation of a benign disease. *Can J Surg.* 2007;50(3):225-226.
17. Eesa M, Kandpal H, Sharma R, Misra A. Spontaneous pneumorrhachis in bronchial asthma. *Acta Radiol.* 2006;47(7):672-674.
18. Faber W, Hirner A, Kaminski M. Unusual cause of pneumomediastinum. *Chirurg.* 2008;79(7):680-681.
19. Forshaw MJ, Khan AZ, Strauss DC, Botha AJ, Mason RC. Vomiting-induced pneumomediastinum and subcutaneous emphysema does not always indicate Boerhaave's syndrome: report of six cases. *Surg Today.* 2007;37(10):888-892.
20. Goh BK, Tan HK, Tan FL, Koong HN. Epidural emphysema associated with spontaneous pneumomediastinum. *Am J Surg.* 2006;192(3):355-356.
21. Hatzitoliou AI, Sion ML, Kounanis AD, et al. Diffuse soft tissue emphysema as a complication of anorexia nervosa. *Postgrad Med J.* 1997;73(864):662-664.
22. Hazouard E, Koninck JC, Attucci S, Fauchier-Rolland F, Brunereau L, Diot P. Pneumorrhachis and pneumomediastinum caused by repeated Müller's maneuvers: complications of marijuana smoking. *Ann Emerg Med.* 2001;38(6):694-697.
23. Hoover LR, Febinger DL, Tripp HF. Rhinolalia: an underappreciated sign of pneumomediastinum. *Ann Thorac Surg.* 2000;69(2):615-616.
24. James M, Miguel M, Fancher T. Spontaneous pneumomediastinum. *J Hosp Med.* 2007;2(4):283-284.
25. Kakitsubata Y, Inatsu H, Kakitsubata S, Watanabe K. CT manifestations of intraspinal air associated with pneumomediastinum. *Acta Radiol.* 1994;35(3):305-306.
26. Koelliker PD, Brannam LA. Epidural pneumatosis associated with spontaneous pneumomediastinum: case report and review of the literature. *J Emerg Med.* 1999;17(2):247-250.
27. Kono T, Kuwashima S, Fujioka M, et al. Epidural air associated with spontaneous pneumomediastinum in children: uncommon complication? *Pediatr Int.* 2007;49(6):923-927.
28. Larena-Avellaneda A, Debus ES, Klein I, Grasshoff S, Höcht B. Epidural pneumatosis and spontaneous pneumomediastinum: differential diagnosis with respect to the Boerhaave syndrome. *Zentralbl Chir.* 2008;133(1):79-81.
29. Manden PK, Siddiqui AH. Pneumorrhachis, pneumomediastinum, pneumopericardium and subcutaneous emphysema as complications of bronchial asthma. *Ann Thorac Med.* 2009;4(3):143-145.
30. Mutlu H, Silit E, Pekkaflali Z, Incedayi M, Başekim C, Kizilkaya E. 'Ecstasy' (MDMA)-induced pneumomediastinum and epidural pneumatosis. *Diagn Interv Radiol.* 2005;11(3):150-151.
31. Nonaka M, Hatakeyama T, Okada I, et al. Epidural pneumatosis associated with pneumomediastinum occurring at rest. *Ann Thorac Cardiovasc Surg.* 2009;15(1):38-41.
32. Oertel MF, Korinth MC, Reinges MH, Gilsbach JM. Pneumorrhachis of the entire spinal canal. *J Neurol Neurosurg Psychiatry.* 2005;76(7):1036.
33. Pangtey GS, Das CJ, Javan N. Airlessness in airspace. Simultaneous occurrence of spontaneous pneumothorax with pneumomediastinum and pneumorrhachis: report of a case. *Surg Today.* 2008;38(1):49-51.
34. Pauw RG, van der Werf TS, van Dullemen HM, Dullaart RP. Mediastinal emphysema complicating diabetic ketoacidosis: plea for conservative diagnostic approach. *Neth J Med.* 2007;65(10):368-371.
35. Pifferi M, Marrazzini G, Baldini G, Caramella D, Bulleri A, Bartolozzi C. Epidural emphysema in children with asthma. *Pediatr Pulmonol.* 1997;24(2):125-126.
36. Pooyan P, Puruckharr M, Summers JA, Byrd RP Jr, Roy TM. Pneumomediastinum, pneumopericardium, and epidural pneumatosis in DKA. *J Diabetes Complications.* 2004;18(4):242-247.
37. Ripley DP, Wilson EJ, Meller MT, Cowlam S. Pneumorrhachis: a rare complication of diabetic ketoacidosis. *Diabet Med.* 2009;26(5):566-567.
38. Sakai M, Murayama S, Gibo M, Akamine T, Nagata O. Frequent cause of the Macklin effect in spontaneous pneumomediastinum: demonstration by multidetector-row computed tomography. *J Comput Assist Tomogr.* 2006;30(1):92-94.
39. Song KJ, Lee KB. Spontaneous extradural pneumorrhachis causing cervical myelopathy. *Spine J.* 2009;9(2):e16-e18.
40. Song Y, Tu L, Wu J. Pneumorrhachis with spontaneous pneumomediastinum and subcutaneous emphysema. *Intern Med.* 2009;48(18):1713-1714.
41. Stull BW. Spontaneous pneumomediastinum following ecstasy ingestion and sexual intercourse. *Emerg Med J.* 2008;25(2):113-114.
42. Tsuji H, Takazakura E, Terada Y, Makino H, Yasuda A, Oiko Y. CT demonstration of spinal epidural emphysema complicating bronchial asthma and violent coughing. *J Comput Assist Tomogr.* 1989;13(1):38-39.
43. van der Klooster JM, Grootendorst AF, Ophof PJ, Brouwers JW. Pneumomediastinum: an unusual complication of bronchial asthma in a young man. *Neth J Med.* 1998;52(4):150-154.
44. van Veelen I, Hogeman PH, van Elburg A, Nielsen-Abbring FW, Heggelman BG, Mahieu HF. Pneumomediastinum: a rare complication of anorexia nervosa in children and adolescents. A case study and review of the literature. *Eur J Pediatr.* 2008;167(2):171-174.

Occupational Asthma Due to Colistin in a Pharmaceutical Worker

Susana Gómez-Ollés, PhD; Federico Madrid-San Martín, MD; María-Jesús Cruz, PhD; and Xavier Muñoz, MD, PhD

To our knowledge, this is the first case report of a 24-year-old man working in a pharmaceutical company transporting and storing raw materials who developed occupational asthma (OA) to colistin. The specific inhalation challenge confirmed the diagnosis of OA to colistin. Specific IgE was not detected, because dot-blot analysis was negative at all colistin concentrations tested. To our knowledge, OA due to a peptide antibiotic has not previously been described. This antibiotic should be listed as a trigger of OA. CHEST 2010; 137(5):1200-1202

Abbreviations: OA = occupational asthma; SIC = specific inhalation challenge

A growing number of pharmaceutical products are being reported as triggers of occupational asthma (OA). Among these are a variety of antibiotics: β -lactams (penicillins and cephalosporins), sulfonamides (sulfathiazoles), and a macrolide antibiotic.¹ This report describes, to our knowledge,

the first case of OA due to colistin, also known as polymyxin E, which is a cyclic polypeptide antibiotic.² To our knowledge, OA due to a peptide antibiotic has not previously been described.

CASE REPORT

A 24-year-old man, a smoker (5 cigarettes/d) since age 18, was employed in a pharmaceutical company transporting and storing raw materials for the last 15 months. He was exposed, among other substances, to methionine, bromhexine, amoxicillin, neomycin, sodium bicarbonate, manganese sulfate, starch, and colistin.

Three months after starting his current job, he developed rhinitis, which improved over the weekends. Nine months after the onset of rhinitis, exposure to colistin caused him to suffer sudden cough, wheeze, and dyspnea. On two occasions, he presented to the ED, and on one of these occasions, he was admitted for 72 h. One month after the second admission, the patient was referred to our department to investigate a possible diagnosis of OA. At this point, he was asymptomatic, and he was not in need of treatment. No abnormality was found during physical examination, chest radiography, or blood testing, and the total serum IgE titer was 33 units/mL. Skin prick tests were positive to *Artemisia* sp and *Alternaria* sp. Lung function showed an FVC of 4.69 L (88%), an FEV₁ of 4.16 L (97%), and an FEV₁/FVC ratio of 88%. The bronchodilator test was negative, and a methacholine concentration of 16 mg/mL was required to produce a 20% decrease in FEV₁. The specific inhalation challenge (SIC) to colistin was performed as described for other pharmaceutical agents³ and was positive, illustrating an early response (Fig 1) with the onset of rhinitis symptoms. Given the possibility that this reaction was related to an irritant effect, the same SIC was conducted on a healthy volunteer exposed to the same inhaled concentration of colistin as the patient, with negative results. A dot-blot experiment was negative to colistin. Briefly, 100, 10, 5, and 1 mg/mL solutions of colistin were prepared. Five microliters of each solution were spotted onto nitrocellulose membranes and air dried. After blocking, the membranes were incubated with diluted patient sera (1:2) for 1.5 h. After three washes, the membranes were incubated for 1 h with biotinylated mouse-antihuman IgE. After further washing, the membranes were incubated for 1 h with streptavidin-horseradish peroxidase. All

the immunoblots were developed with a hemiluminescent substrate.

The patient's work in a colistin-exposed environment was discontinued. At 6-months follow-up, he was asymptomatic, and methacholine testing showed a provocative concentration of methacholine causing a 20% fall in FEV₁ > 32 mg/mL.

DISCUSSION

We have reported the first case, to our knowledge, of OA due to colistin and confirmed by a positive SIC. The combination of the disappearance of asthmatic symptoms and the improvement in airway responsiveness after cessation of exposure, the type of response after the SIC, and no change in lung function in the control subject after the SIC provide evidence for a definitive diagnosis of OA.

On the one hand, the onset of rhinitis symptoms before asthma and the immediate fall in FEV₁ in this patient may suggest the involvement of an IgE-mediated mechanism. On the other hand, the low total serum IgE levels suggest a non-IgE-mediated mechanism. Moreover, the dot-blot assay was negative, so an IgE mechanism was not demonstrated.

OA accompanied by rhinitis symptoms and an immediate response has been described before for several antibiotics,³⁻⁶ but with no IgE mechanism being demonstrated in all studies except by one. In that study, the presence of an IgE mechanism was demonstrated by skin prick test.³ Our findings could be related to the suggestion from Stenton et al⁵ that the development of a determined asthmatic reaction pattern is more dependent on the SIC dose and the degree of airway responsiveness than on any inherent property of the occupational agent.

Because of its high antimicrobial activity against *Pseudomonas aeruginosa*, aerosolized colistin is a potential agent for the treatment of patients with cystic fibrosis.⁷ In this context, several studies have described a bronchoconstriction response in some patients when they are treated with nebulized colistin.⁸⁻¹¹ The mechanism by which colistin may cause bronchoconstriction in patients with cystic fibrosis or lung disease is unknown. However, it has been proposed that the bronchospasm reaction to a nebulized solution

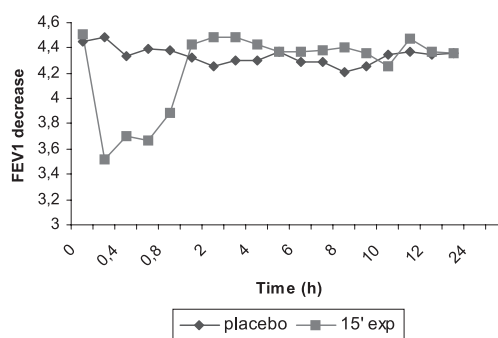


FIGURE 1. Specific inhalation challenge by exposing the subject to 1 g colistin mixed with 49 g lactose. An early asthmatic reaction with a significant fall in FEV₁ was noted at 10 min after the patient was exposed to colistin for 15 min.

Manuscript received August 12, 2009; revision accepted October 13, 2009.

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DOI: 10.1378/chest.09-1881

of colistin could be due to hypertonicity, direct chemical stimulation as occurs in a methacholine challenge test, irritation from chemicals or fumes, allergy in the airway, or nonspecific causes.¹¹

This finding, although only demonstrated with patients with cystic fibrosis, leads us to hypothesize that any patient with asthma may react and have a bronchospasm when exposed to colistin. However, this theory has not been tested, and in the case presented here, although atopic, the patient did not have asthma before being exposed to colistin, and his asthmatic symptoms disappeared after cessation of the colistin exposure.

In conclusion, we have described a case of OA and rhinitis due to inhalation of colistin, a peptide antibiotic. Thus, this antibiotic should be listed as a cause of OA.

ACKNOWLEDGMENTS

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Other contributions: We would like to thank Anenta Ratneswaren for her careful language revision.

REFERENCES

1. Malo JL, Park HS, Bernstein IL. Other chemical substances causing occupational asthma. In: Bernstein IL,

- Chan-Yeung M, Malo JL, Bernstein DI, eds. *Asthma in the Workplace*. 3rd ed. New York, NY: Marcel Dekker; 2006: 555-579.
2. Diot P, Gagnadoux F, Martin C, et al. Nebulization and anti-*Pseudomonas aeruginosa* activity of colistin. *Eur Respir J*. 1997;10(9):1995-1998.
3. Moscato G, Galdi E, Scibilia J, et al. Occupational asthma, rhinitis and urticaria due to piperacillin sodium in a pharmaceutical worker. *Eur Respir J*. 1995;8(3):467-469.
4. Sastre J, Quirce S, Novalbos A, Lluch-Bernal M, Bombín C, Umpiérrez A. Occupational asthma induced by cephalosporins. *Eur Respir J*. 1999;13(5):1189-1191.
5. Stenton SC, Dennis JH, Hendrick DJ. Occupational asthma due to ceftazidime. *Eur Respir J*. 1995;8(8):1421-1423.
6. Malo JL, Cartier A. Occupational asthma in workers of a pharmaceutical company processing spiramycin. *Thorax*. 1988;43(5):371-377.
7. Catchpole CR, Andrews JM, Brenwald N, Wise R. A reassessment of the in-vitro activity of colistin sulphomethate sodium. *J Antimicrob Chemother*. 1997;39(2):255-260.
8. Maddison J, Dodd M, Webb AK. Nebulized colistin causes chest tightness in adults with cystic fibrosis. *Respir Med*. 1994;88(2):145-147.
9. Dodd ME, Abbott J, Maddison J, Moorcroft AJ, Webb AK. Effect of tonicity of nebulised colistin on chest tightness and pulmonary function in adults with cystic fibrosis. *Thorax*. 1997;52(7):656-658.
10. Cunningham S, Prasad A, Collyer L, Carr S, Lynn IB, Wallis C. Bronchoconstriction following nebulised colistin in cystic fibrosis. *Arch Dis Child*. 2001;84(5):432-433.
11. Alothman GA, Ho B, Alsaadi MM, et al. Bronchial constriction and inhaled colistin in cystic fibrosis. *Chest*. 2005;127(2): 522-529.

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