

Bullae, bronchiectasis and nutritional emphysema in severe anorexia nervosa

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VJ Cook, HO Coxson, AG Mason, TR Bai. Bullae, bronchiectasis and nutritional emphysema in severe anorexia nervosa. *Can Respir J* 2001;8(5):361-365.

STUDY OBJECTIVES: Pulmonary complications of anorexia nervosa are rarely documented. The case of a patient with anorexia nervosa and pulmonary disease is presented, a new quantitative computed tomography (CT) method for the detection of emphysema is employed, the literature is reviewed and the concept of 'nutritional' emphysema is discussed.

RESULTS: The case of a 34-year-old, nonsmoking woman with long-standing severe anorexia nervosa who was evaluated for cough and progressive shortness of breath is reported. Pulmonary function testing showed a predominant restrictive pattern with a marked reduction in carbon monoxide transfer and respiratory muscle strength, and an elevated residual volume. Imaging revealed bullae and bronchiectasis, and quantitative analysis of the CT scan was consistent with mild, generalized emphysema. Bronchial washings grew *Pseudomonas aeruginosa*. Known causes for bronchiectasis were excluded. A literature review disclosed few reported noninfectious pulmonary complications of anorexia nervosa.

CONCLUSIONS: To the authors' knowledge, this is the first report of bullae and bronchiectasis in a patient with anorexia nervosa, and the CT analysis was consistent with mild emphysema. Malnutrition has been associated with emphysematous changes in animals and may be the primary insult in the development of emphysema, bullae and bronchiectasis in the present patient.

Key Words: *Chronic obstructive pulmonary disease; Computed tomography; Malnutrition; Lung infections*

Bulles, bronchiectasie et emphysème nutritionnel dans l'anorexie mentale grave

OBJECTIFS DE L'ÉTUDE : Les complications pulmonaires de l'anorexie mentale sont rarement documentées. Le cas d'une patiente anorexique atteinte de maladie pulmonaire est présenté ici. On a eu recours à une nouvelle méthode de scintigraphie pour le dépistage de l'emphysème. La littérature est passée en revue, de même que le concept d'emphysème nutritionnel.

RÉSULTATS : On signale donc le cas d'une non-fumeuse de 34 ans présentant un problème d'anorexie mentale grave de longue date que l'on a examinée pour toux et essoufflement progressifs. Les épreuves de fonction pulmonaire ont montré un tableau surtout restrictif, avec réduction marquée du transfert du monoxyde de carbone, diminution de la force des muscles respiratoires et augmentation du volume résiduel. L'imagerie a révélé la présence de bulles et de bronchiectasie et l'analyse quantitative de la scintigraphie concordait avec un léger emphysème généralisé. L'analyse du liquide de lavage bronchique a révélé la présence de *Pseudomonas aeruginosa*. Les causes connues de la bronchiectasie ont pu être écartées. Une revue de la littérature a permis d'identifier quelques complications non infectieuses associées à l'anorexie mentale.

CONCLUSION : À la connaissance des auteurs, il s'agit du premier cas signalé de bulles et de bronchiectasie chez une patiente atteinte d'anorexie mentale et l'analyse de la scintigraphie concordait avec un léger emphysème. La malnutrition a été associée à des anomalies de nature emphysemateuse chez des animaux et pourrait être le point de départ de l'emphysème bulleux et de la bronchiectasie chez cette patiente.

Anorexia nervosa is a complex and devastating psychosocial disorder that is complicated by metabolic, immunological and endocrine abnormalities during the course of the disease. Of all psychiatric illnesses, it has the highest recorded morbidity and mortality rates. Anorexia nervosa is a disorder characterized by the tetrad of body weight less than 85% of expected, fear of weight gain, disturbance of body image and amenorrhea in postmenarchal females (1). It classically affects young, healthy, white, middle-class women. True prevalence and incidence statistics in North America are unknown, but prevalence has been quoted to be between 0.2% and 1% of the population, and incidence rates have been estimated annually at 7.3/100,000 population (1). The mortality rate in patients with anorexia nervosa is estimated at 0.6%/year. The medical complications of anorexia nervosa are numerous, but pulmonary complications are rare and have not been acknowledged in a recent review (1). We recently encountered a patient with unexpected pulmonary complications, which prompted us to investigate the patient in depth and review the literature. Our investigations led us to re-present the notion of nutritional emphysema – an old but under-recognized concept.

CASE PRESENTATION

A 34-year-old white female patient with long-standing (longer than 16 years), severe anorexia nervosa of the restrictive subtype presented to St Paul's Hospital, University of British Columbia (Vancouver, British Columbia) with progressive shortness of breath and a productive cough. Her respiratory symptoms began at least one year before admission, when she noticed a dry cough. There was increasing shortness of breath on exertion, and weakness and fatigue, which limited her exercise tolerance to less than one block. Before this, she was a regular exerciser, walking hours per day without difficulty. Her cough became productive of creamy yellow sputum, 5 to 10 mL/day. Separate short courses of oral antibiotics did not change her symptoms. She denied hemop-

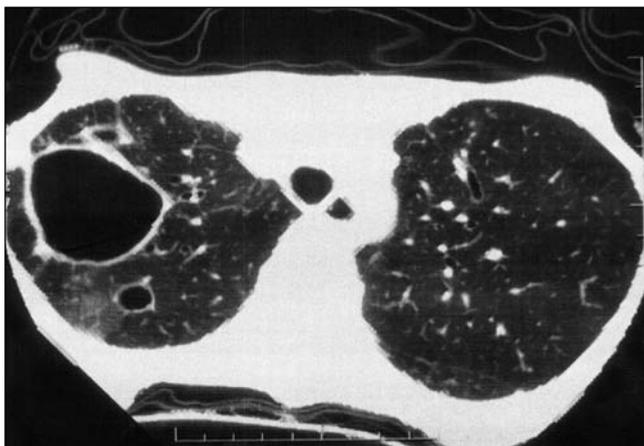


Figure 1 Computed tomography scan of the thorax in the present patient showing multiple bullae in the right upper lobe and cylindrical bronchiectasis in the anterior segment of the left upper lobe

tysis, fever, chills and night sweats. She had no history of tuberculosis, recurrent pneumonia, or toxic exposures or inhalations. She was a lifelong nonsmoker, and denied alcohol and injection drug use. She had no significant travel history and was human immunodeficiency virus (HIV) negative. She had no history of recurrent sinusitis or middle ear problems. She denied purging behaviours, and she had no history of a seizure disorder to suggest aspiration. She kept two healthy budgerigars in her home. She had no known drug allergies, and her medications before admission included hormone supplements, vitamin and mineral supplements, docusate, cisapride and acetaminophen. The only family history of pulmonary disease was that she had a brother with asthma. She lived alone and worked as a pharmacy assistant. As part of previous research protocols of the nutrition service, she had had remote baseline pulmonary function tests and chest radiology.

On examination, she was severely cachectic, weighing only 26 kg. Her height was 161 cm, with a calculated body mass index of 10 kg/m². Her blood pressure was 100/50 mmHg, heart rate was 78 beats/min, respiratory rate was 12 breaths/min, temperature was 35.4°C and cutaneous oxygen saturation was 99% on room air. A head and neck examination showed small cervical lymph nodes. She was neither cyanosed nor clubbed. There was no accessory muscle use or evidence of hyperinflation. Percussion of the chest was normal. On auscultation, she was noted to have diffuse expiratory wheezes and inspiratory crackles localized over the right anterior chest and axillae. There was no bronchial breathing. Her cardiac, abdominal and neurological examinations were normal. Her skin showed multiple areas of breakdown, especially over the bony prominences of her feet.

Investigations: The laboratory parameters showed: white blood cell count $6.7 \times 10^9/L$ with normal differential, hemoglobin 74 g/L, mean corpuscular volume 95 mmol/L, platelet count $469 \times 10^9/L$, sodium 137 mmol/L, potassium 3.9 mmol/L, chloride 99 mmol/L, bicarbonate 29 mmol/L, urea 6.4 mmol/L, creatinine 40 mmol/L, phosphate 0.89 mmol/L, calcium 2.24 mmol/L and magnesium 0.91 mmol/L. Liver enzymes were mildly elevated (aspartate aminotransferase 66 units/L, alkaline phosphatase 157 units/L). Serum albumin was 36 g/L (normal 35 to 50 g/L), and prealbumin was reduced at 104 mg/L (normal 200 to 420 mg/L). Secretory immunoglobulin (Ig) A and alpha₁-antitrypsin levels and sweat tests were normal. Quantitative Ig tests showed normal IgM, mild elevation of IgA at 4.05 g/L (normal 0.68 to 3.78 g/L), and normal IgG subclasses 1, 3 and 4, with mild elevation of subclass IgG₂ at 7.77 g/L (normal 1.17 to 7.47 g/L). Intranasal biopsies showed normal cilia structure at electron microscopy.

A chest radiograph on admission revealed right upper lobe bullous changes and bilateral bronchial wall thickening that was essentially unchanged from appearances four months previously. Bullae were noted to be present on chest radiographs up to three years before admission. A computed tomography (CT) scan of the chest showed no significant

TABLE 1
Quantitative computed tomography analysis for emphysema in the present patient compared with previously published values for control subjects and patients with mild emphysema on histological examination

	Median inflation (mL gas/ g tissue)	Voxels 6.0 to 10.2 mL/g* (%)	Voxels greater than 10.2 mL/g [†] (%)	Surface area/ Volume (cm ² /mL)	Surface area (m ²)
Control subjects	4.4±0.1	20±3	1±0	300±9	128±5
Mild emphysema cohort	5.8±0.3 [‡]	35±4 [‡]	13±1 [‡]	212±12 [‡]	119±3 [‡]
Patient	6.8±1.3	39	18	170	62

*6.0 to 10.2 mL/g is between -856 Hounsfield units (HU) and -910 HU, and corresponds to emphysematous lesions smaller than 5 mm in diameter; [†]Greater than 10.2 mL/g is less than -910 HU and corresponds to emphysematous lesions larger than 5 mm in diameter; [‡]P<0.05 versus controls. Data from reference 2

lymphadenopathy and confirmed a large right apical thick-walled bulla larger than 6 cm in diameter, with smaller adjacent bullae (Figure 1). Numerous nodular densities were noted in the lung zones diffusely, primarily centrilobular, with characteristic tree-in-bud forms consistent with retained small airway secretions. Dilated peripheral airways and bronchial wall thickening indicative of cylindrical bronchiectasis were noted bilaterally in both upper and lower lobes.

A new CT quantitative technique developed at the University of British Columbia, which has been used successfully to predict lung surface-to-volume ratio and surface area, and correlates with emphysema, was then used (2,3). Computer images were obtained using a high resolution CT scanning technique with a field of view of 25.5 cm, a thickness of 0.1 cm and a gap of 1.0 cm on a GE 9800 Highlight Advantage (GE Medical Systems, USA) CT scanner. The lung parenchyma, excluding the bullae, and the major vessels and airways were analyzed. The patient's lung surface-to-volume ratios were compared with values published from the University of British Columbia for control patients and patients with mild emphysema (2). The values determined for the present patient were suggestive of mild emphysema, because by definition, greater than 5% but less than 20% of her lung voxels were above 10.2 mL/g (Table 1).

Pulmonary function studies (Table 2) were performed using standard techniques and compared with results obtained on the same apparatus in 1993. Residual volume was determined using the helium dilution technique, and single-breath diffusion capacity of the lung for carbon dioxide (DLCO) was measured in duplicate and corrected for anemia. The patient refused body plethysmographic measurement of lung volumes. Testing followed the standards of the American Thoracic Society. The results showed a predominantly restrictive pattern, with reduction in vital capacity and total lung capacity. Residual volume was increased both in 1993 and 1999, suggesting early airway closure or muscle

TABLE 2
Pulmonary function test results in our patient in 1993 and 1999

	1993 (weight 29 kg), actual	1993, % predicted	1999 (weight 25 kg), actual	1999, % predicted
FVC	2.37	63	1.35	38
FEV ₁ *	2.20	67	1.20	40
FEV ₁ /FVC	0.93		0.89	
SVC	2.34	62	1.38	39
FRC	2.71	80	2.47	73
RV	2.21	140	1.95	125
TLC	4.55	85	3.33	65
DLCO	16.39 [†]	65	8.97 [‡]	37
DLVA	4.34	74	3.24	51

*No response to bronchodilator; [†]Corrected for a hemoglobin of 70 g/L; [‡]Corrected for a hemoglobin of 80 g/L, using a formula from reference 26. See text for respiratory muscle testing results in 1999. DL Diffusion capacity of the lung; DLCO Diffusion capacity of the lung for carbon dioxide; FEV₁ Forced expiratory volume in 1 s; FRC Functional residual capacity; FVC Forced vital capacity; RV Residual volume; SVC Slow vital capacity; TLC Total lung capacity; VA Alveolar volume

weakness. There was no response to bronchodilators, and the flow-volume curve did not suggest expiratory airflow obstruction. DLCO corrected for her level of anemia was markedly reduced, more so than in 1993. Respiratory muscle testing showed a marked reduction in maximal inspiratory and expiratory muscle force (maximum inspiratory pressure 22 cm H₂O, maximum expiratory pressure 34 cm H₂O).

At bronchoscopy, marked pallor and apparent thinning of the bronchial mucosa was noted, but there was no endobronchial obstruction. The bronchoalveolar lavage specimen showed a marked polymorphonuclear cell increase, along with reactive columnar epithelial cells. Bronchial washings grew *Pseudomonas aeruginosa*, and treatment was started with intravenous ceftazidime for two weeks and then oral ciprofloxacin to complete six weeks of therapy. Mycobacterial cultures were negative.

DISCUSSION

Pulmonary complications of anorexia nervosa are rarely reported in the literature, and to our knowledge, this is the first report of bullae underlying emphysema and bronchiectasis. Although a causal relationship has yet to be determined, we propose that these complications are secondary to the severe prolonged malnutrition evident in our patient.

The results of experiments in protein-restricted rats show histopathological changes consistent with emphysema (4,5), a concept referred to as 'nutritional emphysema'. Starvation also worsens existing emphysema in rats. In the Warsaw, Poland ghettos during World War II, autopsy studies showed emphysema in malnourished young adults without any underlying lung disease or history to explain these changes (6). In our patient, there is evidence for emphysema on pulmonary function testing, as seen in the reduced

DLCO tests and on quantification of lung surface area by CT scan. A recent report of pulmonary function testing in a cohort of patients with anorexia nervosa (7) showed decreased inspiratory and expiratory muscle strength and increased residual volume, as in our patient, but normal DLCO. However, we documented a marked diffusion abnormality even when corrected for hemoglobin and alveolar volume. The reduction in diffusing capacity, combined with the CT abnormalities, suggests a significant loss of alveolar capillary surface area consistent with the parenchymal destruction of emphysema. Our patient had a much longer duration of severe anorexia than the patients studied by Pieters et al (7), who had a median duration of illness of only 4.5 months.

Although the elevated residual volume may be secondary to expiratory muscle weakness alone, a component secondary to early closure of small airways accompanying early emphysema cannot be excluded. An apparent reduction in respiratory rate, tidal volume and oxygen consumption, as well as a weakness of the muscles of respiration, has been reported by others (8). In addition, a patient with severe hypophosphatemia from anorexia nervosa has been described, which manifested as generalized muscle weakness and bulbar muscle dysfunction, resulting in aspiration and cardiorespiratory arrest (9). Pneumomediastinum, subcutaneous emphysema, epidural emphysema and interstitial emphysema have all been reported in anorexia nervosa (10-12). Pneumomediastinum secondary to esophageal tears from excessive vomiting has also been reported. How malnutrition alters the lung parenchyma is unknown. Malnutrition leading to weakness of the alveolar wall and eventual rupture is the proposed mechanism in reports of soft tissue emphysema seen in anorexia nervosa (10,11). An inflammatory cell influx in a milieu of imbalance between proteinases and antiproteinase activity probably causes the destruction of alveolar walls in emphysema due to tobacco smoking. There is evidence suggesting that there are antioxidant deficiencies, reduced numbers of functioning alveolar macrophages, and reduced production and secretion of surfactant in anorexia nervosa and other dietary disorders (13,14). In the HIV population, there are reports of emphysematous-like changes in the lungs of patients without underlying lung disease (15). However, these patients also had severe wasting, so that the emphysematous changes may be, in part, related to malnutrition, although virus-induced changes may be more important in this group. HIV is also associated with bronchial dilation (16) and premature bullous disease (17,18).

By examining the patient's history, physical well-being and laboratory studies, we were unable to link any of the common causes of bronchiectasis with our patient. Related to the bingeing and purging behaviours seen in some patients with anorexia nervosa, there have been reports of aspiration pneumonitis or pneumonia (19). Our patient gave no history of recurrent pulmonary infection and denied purging, and bronchiectasis after focal pneumonia was thought to be less likely because of the diffuse changes seen on the CT scan. She had no detectable abnormality in host defenses: her cil-

ial structure and sweat test results, and her quantitative Ig, alpha₁-antitrypsin and secretory IgA levels were normal. However, we have not ruled out a mild mutation in the CFTR gene that could predispose the patient to bronchiectasis in the presence of a normal sweat chloride. Also, T-cell function was not formally assessed, but total leukocyte counts and differential were normal. At the time of presentation, her airways were colonized with *P aeruginosa*. We suspect that this pathogen, although capable of causing necrotizing pneumonia, was not responsible for her bullae, because these were noted on chest radiography two years before the onset of symptoms, although it is possible that the bullae were a consequence of subacute infection by Gram-negative organisms such as *P aeruginosa*. Of note, her foot ulcers did not grow *P aeruginosa*.

The immune status of patients with anorexia nervosa is an area of conflict in the literature. Hematological and immunological abnormalities such as bone marrow hypoplasia and neutropenia, reversible granulocyte bactericidal defects, hypocomplementemia, cutaneous anergy and elevated cortisol have all been documented in patients with anorexia nervosa (13,20,21). However, despite documentation of low levels of Igs and complement, functional responses of patients with anorexia nervosa seem well preserved, in that serious infections are rare, particularly viral infections, and there has been no documented increased incidence of community-acquired pneumonia or opportunistic infections. One possible explanation is that anorexia nervosa is a carbohydrate-deficient state with adequate protein stores, whereas infection related to malnutrition is well documented in protein-calorie malnutrition, as seen in patients with kwashiorkor, who have low levels of cell-mediated and humoral-mediated immunity (22,23). However, it has been postulated that anorexia nervosa may predispose patients to unusual infections with organisms of lower pathogenicity, such as the *Pseudomonas* species seen in our patient (13).

Tuberculous disease is the most common pulmonary infection linked to anorexia nervosa (1,21,24). Nontuberculous mycobacterial infection has also been reported (20). Impaired ventilatory responses during starvation have been hypothesized to contribute to the increase in tuberculosis seen in these patients (13), although compromised cell-mediated immunity is more likely to be responsible (25).

CONCLUSIONS

We present evidence that the malnourished state associated with anorexia nervosa negatively affects the respiratory system. The present patient is likely to be at an increased risk for further pulmonary complications such as pneumothorax and recurrent infections. The concept of nutritional emphysema in this patient population could be further established in a cohort of patients with various degrees of malnutrition using the CT approach outlined above.

ACKNOWLEDGEMENTS: The authors' research is supported by the British Columbia Lung Association.

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