Near-fatal Anorexia Nervosa in a Middle-aged Woman

Luca Foppiani, Bruno Massobrio, Christian Cascio and Giancarlo Antonucci

Abstract

Anorexia nervosa (AN) is a serious psychiatric disorder which typically occurs in young women; however, more and more cases in middle-aged women are being reported. The management of this complex disease requires a team approach, and full recovery occurs only in 50% of patients. Endocrine and metabolic complications are commonly observed, the latter of which may even be life-threatening, and require prompt and proper management. Infections, albeit reported, are not usually a major clinical problem in these patients. We herein report the case of a severely malnourished middle-aged woman with long-standing AN who was hospitalized with marked hypokalaemia (1.5 mEq/L) and rhabdomyolysis; during hospitalization she developed septic shock and acute respiratory distress syndrome, which required urgent admission to the intensive care unit. She underwent sedation and tracheal intubation for mechanical ventilation and was managed with combined therapies, which eventually led to a successful outcome. Life-threatening medical complications can occur not only in young women but in middle-aged women with AN as well and require a combined multidisciplinary approach.

Key words: anorexia nervosa, hypokalaemia, ARDS, intensive care unit

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Introduction

Anorexia nervosa (AN) is a psychiatric disorder which can result in life-threatening medical complications (1-3) and multifaceted endocrine abnormalities (4, 5). Its prevalence is 0.2-0.9% among young women, with a peak age ranging between 14 and 25 years (1). However, a significant number of middle-aged women have this disorder as well, including those who never recovered from adolescent AN and, to a lesser extent, those who develop this disorder for the first time in middle age (6).

The treatment of AN is difficult and requires a multidisciplinary team that includes a psychiatrist or psychologist, an internist/endocrinologist, and a nutritionist. Despite multidisciplinary treatment efforts, the overall prognosis is quite poor, with only 40% to 50% of AN patients progressing to complete recovery (1, 5). Despite being severely malnourished, AN patients have fairly well-preserved immune function and are relatively free from infectious diseases (7-9). However, cases of infections, some severe and mostly in the lung, have been reported (10-12).

Case Report

A 46-year-old woman was taken to the emergency department of our hospital by the territorial emergency team after she had been found on the floor in her house by a friend; the patient reported that she had fallen because her legs “had given way” and that she was unable to stand up. A physical examination showed that the patient was fully conscious but cachectic and dehydrated, and she had low blood pressure (75/50 mmHg) with bruises on the chin and right hip. Electrocardiography (ECG) revealed sinus bradycardia (60 bpm) with a prolonged corrected QT interval (0.60 sec). Hemogasanalysis showed metabolic hypokalaemic hypo-chloroaemic alkalosis (pH: 7.7, n.v. 7.35-7.45, PO2: 100 mmHg, n.v. 80-100, pCO2: 38 mmHg, n.v. 35-45, K: 1.7...
body weight: 25.7 kg, body mass index (BMI): 10.7 Kg/m². Parameters revealed severe malnourishment [height: 155 cm, AN purging subtype.}

beit infrequently. Overall, the patient’s habits characterized stipation. In addition, she reported self-induced vomiting, al-

supervised by a psychiatric centre until two years prior and

malnutrition, alcoholism, and suicide attempts. She had been

years earlier, and several previous hospital admissions for

sis ascertained a long history of AN, diagnosed about 20

hospitalized in the Internal Medicine Department. Anamne-

sion (90 mEq) in saline was started, and the patient was

advised admission to a medical facility. A potassium infu-

vis, and facial bones proved unremarkable. The psychiatrist

advised admission to a medical facility. A potassium infu-

vis, and facial bones proved unremarkable. The psychiatrist

Her last menses dated back 13 years. The physical pa-

ters revealed severe malnourishment [height: 155 cm, body weight: 25.7 kg, body mass index (BMI): 10.7 Kg/m²], dehydration and low blood pressure (80/60 mmHg). The woman, who was poorly cooperative, reported not having eaten or drunk in the previous few days.

Further laboratory testing was carried out for biochemical and hormonal evaluations (Table). Her gonadotropin levels, which were associated with undetectable 17β-estradiol levels, were unexpectedly elevated given the patient’s extreme malnutrition and were compatible with a menopausal state; in addition, reduced IGF-I levels, sick euthyroid syndrome and secondary hyperparathyroidism with undetectable vita-

min D levels were ascertained. Her cortisol levels were sur-

prisingly normal for a severely malnourished subject, whereas the nutritional parameters were obviously reduced.

Her resting energy expenditure (REE) was calculated us-

ing the Harris-Benedict formula as 965 kcal/day. Saline (250 mL/day) and partial parenteral nutrition (PPN) (volume: 1,500 mL, 1,000 kcal, with glucose, amino acids, lipids, and electrolytes supplemented with vitamins) was started at a low infusion rate, with the total caloric amount administered in 72 hours for the first 3 days, in 48 hours from days 4 to 6 and every 24 hours thereafter. In addition, a balanced diet was started and was slowly increased up to 1,500 kcal/day with good tolerance. Prophylactic low-molecular weight heparin, proton-pump inhibitors, intravenous ceftriaxone, and oral colecalficérol (100,000 IU as initial load and 10,000 IU/week thereafter) were also started. Large amounts of infused potassium (up to 120 mEq/day) were required to normalize serum levels in 5 days; the corrected QT interval subsequently normalized on ECG. Her haemoglobin (Hb) levels dropped to 7.3 g/dL, without apparent blood loss, probably as a result of haemodilution, and 1 unit of packed red blood cells was transfused which increased the Hb levels (8.7 g/dL). A central venous catheter was positioned in or-

der to properly continue the combined therapies, and a slow but constant improvement in the patient’s clinical condition was observed, although mild oedema occurred in her legs. Owing to this appropriate management, no refeeding syn-
drome occurred, and the patient gained 2 kg in weight in 2 weeks. However, over several days, the patient developed acute urinary retention with marked bladder overdistension (1,700 mL), for which she was catheterised, and an acute confusional state requiring urgent computed tomography (CT) of the brain, which showed cerebral atrophy and cere-

brovascular disease (Fig. 2). However, these symptoms van-

ished spontaneously.

Three weeks after admission, the patient became febrile, and septic shock with acute respiratory failure and oliguria rapidly ensued; she appeared to have multorgan failure syn-
drome. Hemogasanalysis with ambient air revealed hypoæx-

mia (PO2: 51 mmHg) with normocapnia (PCO2: 29.4 mmHg), PO/FiO2: 242, SO2: 88%, reduced HCO3-: 20.4 mEq/L, and pH: 7.45. An urgent chest X-ray examination showed bilateral interstitial pneumonia (Fig. 1b), and urgent laboratory testing revealed markedly increased CRP levels (30.9 mg/dL) and procalcitonin levels (17.1 ng/mL), in-

increased creatinine levels (2.4 mg/dL), and reduced Hb levels (7.6 g/dL) (Table). Blood and urine cultures were negative for HIV antibodies, Mycoplasma pneumoniae antibodies, and urinary antigen for Legionella pneumophila. One unit of packed red blood cells was transfused, and colloids, crystal-

loids, broad-spectrum antibiotic therapy (intravenous piper-

cillin/tazobactam), steroids, and oxygen were started. The patient’s respiratory condition, as assessed by hemogasanaly-

sis (PO2: 46.3 mmHg, PCO2: 38.3 mmHg, PO/FiO2: 193, SO2: 83%, HCO3-: 22.1 mEq/L, pH: 7.37), worsened further. ARDS was diagnosed, and continuous positive airway pres-

sure [CPAP, FiO2: 60%, positive end-expiratory pressure (PEEP): 5 cm H2O] was started but proved unsuccessful.

After an anaesthesiological evaluation of the patient, whose clinical condition was by now critical, she was ur-

gently transferred to the ICU, where she underwent sedation and endotracheal intubation for mechanical ventilation. In addition to the therapies she was already receiving, she was started on a dopamine and norepinephrine infusion due to persistent hypotension. She also received intravenous albu-

min, calcium, sodium bicarbonate, and diuretics. The he-

mogasanalysis values deteriorated (CPAP, FiO2: 60%, PEEP: 7 cm H2O) and revealed respiratory acidosis (pH: 7.187, PO2: 46.2 mmHg, PCO2: 75.6 mmHg, HCO3-: 28.6 mEq/L, PO/FiO2: 71, markedly reduced). A further chest X-ray ex-

amination revealed a worse picture than that seen 2 days earlier, showing bilateral diffuse interstitial-alveolar consolida-

dations with no evidence of ventilation (Fig. 1c). PEEP was progressively increased to 12 cm H2O and, in order to im-

prove oxygenation and mitigate the harmful effects of me-

chanical ventilation, cycles of ventilation in the prone posi-

tion were started. Blood cultures proved positive for Enterococcus faecalis and Candida albicans, and antibiotic therapy was implemented with parenteral linezolid and fluconazole on the advice of an infectivologist. Echocardiography was normal.
Table. Main Laboratory Tests throughout Hospitalization in the Middle-aged Woman with Anorexia Nervosa Studied.

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<td>Glucose (n.v. 70-115 mg/dL)</td>
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<td>65</td>
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<td>144</td>
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<td>78</td>
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<td>194</td>
<td>178</td>
<td>121</td>
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<td>Creatinine (n.v. 0.6-1 mg/dL)</td>
<td>1.4</td>
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<td>Na (n.v. 135-145 mEq/L)</td>
<td>125</td>
<td>134</td>
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<td>139</td>
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<td>K (n.v. 3.5-5 mEq/L)</td>
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<td>AST (n.v. 4-37 IU/L)</td>
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<td>67</td>
<td>42</td>
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<td>71</td>
<td>53</td>
<td>166</td>
<td>77</td>
<td>68</td>
<td>103</td>
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<td>ALT (n.v. 4-41 IU/L)</td>
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<td>CPK (n.v. 39-208 IU/L)</td>
<td>1,159</td>
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<td>392</td>
<td>142</td>
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<td>48</td>
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<td>Calcium (n.v. 8.2-10.2 mg/dL)</td>
<td>7</td>
<td>7.6</td>
<td>8.4</td>
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<td>8.1</td>
<td>7.3</td>
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<td>Phosphorus (n.v. 2.7-4.5 mg/dL)</td>
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<td>Magnesium (1.6-2.6 mg/dL)</td>
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<td>White blood cells (n.v. 4,000-11,000/mL)</td>
<td>12,280</td>
<td>6,520</td>
<td>4,540</td>
<td>5,060</td>
<td>6,220</td>
<td>7,850</td>
<td>7,440</td>
<td>4,690</td>
<td>4,350</td>
<td>11,270</td>
<td>17,050</td>
<td>22,460</td>
<td>24,570</td>
<td>22,710</td>
<td>19,870</td>
<td>14,650</td>
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<tr>
<td>Neutrophils (n.v. 2,000-8,000/mL)</td>
<td>10,450</td>
<td>4,790</td>
<td>2,950</td>
<td>2,700</td>
<td>3,710</td>
<td>5,610</td>
<td>4,640</td>
<td>3,670</td>
<td>3,500</td>
<td>9,230</td>
<td>14,570</td>
<td>18,470</td>
<td>22,160</td>
<td>19,410</td>
<td>17,570</td>
<td>13,050</td>
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<td>Haemoglobin (n.v. 14-17 g/dL)</td>
<td>8.8</td>
<td>9.5</td>
<td>9.1</td>
<td>7.3</td>
<td>8.7</td>
<td>10.4</td>
<td>9.6</td>
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<td>11.2</td>
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<td>10.9</td>
<td>10.2</td>
<td>10.3</td>
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<td>8.7</td>
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<td>Hematocrit (n.v. 42-50%)</td>
<td>22.8</td>
<td>25.9</td>
<td>23.9</td>
<td>20.3</td>
<td>24.8</td>
<td>31.5</td>
<td>28.4</td>
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<td>26</td>
<td>32.4</td>
<td>36.7</td>
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<td>30.5</td>
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<td>25.1</td>
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<td>MCV (n.v. 80-96 fl)</td>
<td>88.4</td>
<td>90.6</td>
<td>96.5</td>
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<td>90.8</td>
<td>89.2</td>
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<td>88.6</td>
<td>90.2</td>
<td>84.4</td>
<td>84</td>
<td>88.6</td>
<td>86.2</td>
<td>8.5</td>
<td>85.9</td>
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<td>Platelets (n.v. 150,000-400,000/mL)</td>
<td>123,000</td>
<td>137,000</td>
<td>134,000</td>
<td>88,000</td>
<td>91,000</td>
<td>92,000</td>
<td>301,000</td>
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<td>131,000</td>
<td>138,000</td>
<td>130,000</td>
<td>86,000</td>
<td>147,000</td>
<td>187,000</td>
<td>158,000</td>
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<td>Iron (30-200 µg/dL)</td>
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<td>Ferritin (n.v. 30-400 ng/L)</td>
<td>1,006</td>
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<td>Prothrombin time (n.v. 70-120%)</td>
<td>62</td>
<td>79</td>
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<td>Albumin (n.v. 3.5-5.2 g/dL)</td>
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<td>Transferrin (n.v. 200-400 mg/dL)</td>
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<td>Haemoglobin (20-30 mg/dL)</td>
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<td>IgG (n.v. for age 90-360 mg/ml)</td>
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<td>FT4 (n.v. 0.93-1.7 ng/ml)</td>
<td>0.68</td>
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<td>FT3 (n.v. 1.8-4.6 pg/ml)</td>
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<td>TSH (n.v. 0.3-4.2 µU/mL)</td>
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<td>LH (7.7-7.85 mIU/mL for menopause)</td>
<td>77.2</td>
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<tr>
<td>FSH (25.8-134.8 mIU/mL for menopause)</td>
<td>168.9</td>
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<td>17-beta-oestradiol (&lt;20 pg/ml for menopause)</td>
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<td>PRL (n.v. 3-20 ng/mL)</td>
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<td>Cortisol (n.v. 6.2-19.4 µg/dL, 7-10 a.m.)</td>
<td>14.5</td>
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<td>25-OHD (n.v. &gt; 30 ng/mL)</td>
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<td>PTH (n.v. 15-65 pg/mL)</td>
<td>174.4</td>
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<td>CRP (n.v. 0.0-0.5 mg/dL)</td>
<td>3.1</td>
<td>2.2</td>
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<td>PCT (&lt;0.5 ng/mL)</td>
<td>17.1</td>
<td>22.8</td>
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<td>pro-BNP (&lt; 500 pg/mL)</td>
<td>70,000</td>
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<td>Ethanol (g/L)</td>
<td>negative</td>
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<tr>
<td>HIV test</td>
<td>negative</td>
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(continue)
Over several days, 2 units of packed red blood cells were transfused in response to relapsing anemia (Hb: 6.6 g/dL). The patient's clinical condition, laboratory data (reduction in CRP and procalcitonin levels, normalization of renal
wean her off sedation proved ineffective, owing to psychosomatic blood cultures) (Table), and chest X-ray findings (Fig. 1d) slowly improved. However, several attempts to wean her off sedation proved ineffective, owing to psychomotor agitation and subsequent desaturation; on one occasion, generalized seizure occurred after the withdrawal of sedation, and intravenous levetiracetam and intramuscular phe-noobarbital were started. Electroencephalography (significant high-grade diffuse alterations of electrical activity) and CT scan (known cerebral atrophy) were performed.

Two weeks after admission to the ICU, sedation was gradually tapered off. The patient was eventually extubated and resumed spontaneous breathing, but oxygen therapy (6 L/min by Ventimask) was necessary in order to obtain satisfactory oxygen saturation. Although reduced, interstitial-alveolar consolidations persisted on chest X-ray (Fig. 1e). A nasogastric tube was placed, and enteral nutrition was started. The patient was transferred to the critical-care medicine ward, where, after a few days, the nasogastric tube was removed and medical therapies (parenteral nutrition, antibiotics, antiepileptics, proton-pump inhibitors, benzodiazepines, oxygen therapy) were continued. Careful oral re-alimentation with a balanced diet was started. The chest X-ray findings markedly improved, showing only small right alveolar consolidations (Fig. 1f). Oxygen therapy by nasal cannula was withdrawn, and the oxygen saturation in the air

Figure 1. The patient's chest X-ray findings throughout hospitalization. On admission, no lung pathologies were observed (a). During hospitalization, the patient developed septic shock and ARDS, and bilateral interstitial pneumonia (mainly in the right middle-basal and left parahilar regions) was found. CVC is visible along the projection of the left subclavian vein (arrow) (b). The lung condition quickly worsened after admission to the ICU, with findings of bilateral diffuse interstitial-alveolar consolidations and no evidence of ventilation (c). Following the initiation of combination therapies, the lung picture partially improved, and bilateral ventilation resumed (d). After extubation, accentuated hilar and perihilar vascular images and reduced transparency due to interstitial-alveolar consolidations, mainly in the right lung, were observed (e). Over the following days, the lung picture markedly improved, with persistence of only minor alveolar consolidations at the middle right site and stasis of the small pulmonary circulation (f). ARDS: acute respiratory distress syndrome, CVC: central venous catheter, ICU: intensive care unit

Figure 2. The patient's basal CT of the brain showing cerebral atrophy and cerebrovascular disease. CT: computed tomography
remained normal. One more unit of packed red blood cells was infused due to anemization (Hb: 7.6 g/dL); afterwards, her Hb levels remained stable (Table). One week later, the patient was transferred back to our internal medicine ward.

Her clinical condition was significantly improved, respiratory function was satisfactory, body weight had increased (to 32.6 kg; +25% vs. baseline, BMI: 13.6 kg/m²), and nutrition and endocrine parameters were consequently enhanced (Table). After a few days, during which her therapies were continued, the patient, still severely malnourished but in a stable cardio-respiratory condition and with satisfactory metabolic parameters (Table), was discharged and transferred to a specialized centre for rehabilitation. In total, the patient was hospitalized for two months.

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Discussion

AN is a relatively common disorder among young women. While the age- and sex-adjusted incidence rates calculated from the general practice databases (4.7-7.7 per 100,000 person-years) have remained remarkably stable over the last 20 years, there has been an increase in the incidence in the high-risk-group of 15-19-year-old girls (1). However, AN among middle-aged and older women is relatively rare (6). Its prevalence in women 40-60 years of age ranges from 0.4% in Europe to 1.6% in the USA (6). AN in middle-aged and older women is therefore deemed to be mainly a chronic presentation of a disorder with earlier onset (6).

AN has the highest rate of mortality among mental disorders, with an overall standardized mortality ratio ranging from 5 to 12 (1, 12, 13), a substantial portion of which (approximately 20%) is attributable to the suicide rate (13-56 times that expected for a similar age and sex) (5, 13). Alcoholism, which was present in our patient’s history, is an independent risk factor for mortality (5, 13). Life-threatening medical complications (mostly metabolic and cardiac) play a major role in the increased mortality of these patients (2, 13). In our AN patient, the misuse of laxatives and occasional self-induced vomiting caused metabolic hypokalaemic hypochloraemic alkalosis, with dramatically low potassium levels (<2 mEq/L). These metabolic findings indicate Pseudo-Bartter’s syndrome, which is characterized by the activation of the renin-angiotensin-aldosterone system secondary to volume depletion triggered by purging/vomiting (14). However, the plasma renin activity and plasma aldosterone concentration were not measured in the present case.

A peculiar feature of AN patients is their gradual adaptation to weights which may even be dramatically low (BMI in the range of 9-12 kg/m²) together with a fairly adequate availability of macro- and micronutrients; this distinguishes AN from the protein-specific malnutrition observed in famines (15). Whether this capacity is due only to a reduction in lean body mass or, as is more likely, to active mechanisms that reduce energy expenditure (e.g., euthyroid sick syndrome with decreased T3 levels and increased reverse T3 levels, a decreased cardiovascular function and leptin levels) remains unclear (15). Under typical conditions of starvation, the diet is deficient in both proteins and vitamins. AN patients, however, are primarily deficient in carbohydrates and fats but have fairly adequate protein and vitamin intake (6, 8). This relatively normal protein intake might contribute to the absence of increased susceptibility to infections in AN patients, since the blunted immune response to mitogens is more related to protein deficit than to overall reduced calorie intake (7).

In this regard, interesting results have emerged from a recent study conducted in a small group (n=15) of young (age range: 15-24 years) AN women. Although these patients displayed a reduced number (and impaired bioenergetic metabolism) of several immune cell populations (leucocytes, lymphocytes and NK cells), these cells were seen to have higher antioxidant potential and greater resistance to stress than those of age-matched controls, suggesting a preserved immune function; in addition, an increased anti-inflammatory status (i.e., increased serum adiponectin levels) was found in these patients (9).

Old literature data suggest that malnutrition may suppress infections, while refeeding may activate them (7). Indeed, a reduction in iron intake and, more importantly, its sequestration in the liver (as indirectly inferred from our patient’s increased ferritin levels on admission) and spleen can reduce bacterial proliferation. This sort of protection may be lost during the refeeding phase, as a result of the increased metabolic requests of electrolytes, micronutrients, and vitamins essential for the preservation of cellular immunity (7). After three weeks of re-alimentation (both parenteral and oral) without biochemical or clinical signs of refeeding syndrome, our patient developed septic shock due to gram-positive cocci and yeasts, as well as interstitial pneumonia (no etiological pathogen was found) causing ARDS and urgent admission to the ICU.

As described in early reports, in AN patients, the lung may be affected by microorganisms that are often non-pathogenic (Mycobacterium subtypes) (10) or uncommon (e.g., Aspergillus spp.) (11) in normonourished people. Although infrequent, lung infections in AN patients may be severe. In this regard, it has been suggested that malnutrition may i) cause sympathetic suppression and hence blunt the hypoxic ventilatory response; ii) reduce the mass of respiratory muscles (mainly diaphragm), thereby impairing respiratory dynamics; or iii) increase proteinase activity, thus damaging the connective tissue of the lung (10).

ARDS is a severe, life-threatening medical condition characterized by bilateral pulmonary infiltrates and triggered by a variety of systemic or pulmonary injuries, with severe hypoxaemia ensuing. Despite medical progress in the management of ARDS, the mortality remains high, ranging from 27% to 58%, although advances in supportive care have led to improved outcomes in recent years (16, 17).
In our AN patient, severe ARDS (PO2/FiO2<100) was triggered by both interstitial pneumonia and sepsis secondary to multipathogens and required urgent admission to the ICU, followed by sedation and intubation for mechanical ventilation. Combined therapies involving the administration of fluids, broad-spectrum antibiotics, antimycotics, inotropics, steroids, and antiepileptics (to treat seizures) eventually led to a successful outcome. Our patient had a long-standing history of AN and was extremely malnourished, showing several endocrine alterations found in this disorder (although also present in other types of malnutrition) such as reduced IGF-I levels and sick euthyroid syndrome (4, 5). All of these parameters improved with weight gain. Surprisingly, given her extreme underweight condition, hypergonadotrophic (not hypogonadotropic) hypogonadism was found; this was associated with the patient’s undetectable estradiol levels and was compatible with a menopausal state. In addition, her cortisol levels (expected to be elevated in AN) were normal, probably owing to reduced liver production of corticosteroid-binding globulin secondary to severe malnutrition (18).

With regard to refeeding management, on admission, the patient’s REE was calculated using the Harris Benedict formula, which is known to be flawed in AN since it overestimates REE by up to 20% in comparison with indirect calorimetry (19). A combination of refeeding through both PPN and gradually increasing the oral balanced diet was started. As previously recommended (albeit currently under debate), the initial amount of calorie intake administered in our AN patient was as low as 10 kcal/kg/day and progressively increased to 90 kcal/kg/day without biochemical or clinical signs of refeeding syndrome (20, 21). Regarding this progressive diet, current understanding holds that AN patients (particularly those with restricting type) tend to require stepwise escalation in their caloric intake to maintain a 1- to 1.5-kg/week weight gain, starting from 20-30 kcal/kg/day and increasing to 60-100 kcal/kg/day to show sustained weight gain (22).

In her time in the ICU, the patient underwent total parenteral nutrition during the intubation phase; after extubation, enteral nutrition by means of a nasogastric tube was used. As soon as the patient’s clinical condition had improved, she was returned to the internal medicine ward, where oral re-alimentation was carefully started.

In our middle-aged patient with a long-standing history of AN, combined and careful intensive medical management of severe medical complications, in both the internal medicine department and the ICU, prevented a fatal outcome. On discharge, although her clinical condition had significantly improved, the patient was still seriously underweight and was transferred to a rehabilitation centre to continue her treatment.

In conclusion, AN may have dramatic consequences on the health, even in middle-aged women, owing to the possible occurrence of life-threatening medical complications. Every effort must be made by the medical community to detect the manifestations of AN promptly and to coordinate the work of various specialists in order to implement appropriate combined therapies with long-term follow-up.

The authors state that they have no Conflict of Interest (COI).

References