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Multiple organ failure and coma as initial presentation of pheochromocytoma in a patient with multiple endocrine neoplasia (MEN) type II A

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Abstract. The unusual case of a 65-year-old woman with intermittent hypotension, fever, pulmonary edema and coma as initial presentation of pheochromocytoma is reported. The patient developed respiratory, cardiac and renal failure, disseminated intravascular coagulation and liver dysfunction. She had to be defibrillated on multiple occasions, occurring in periods of severe hypertension. After successful surgical removal of a pheochromocytoma a thyroid medullary carcinoma was detected. Several members of the patients family had presented with multiple endocrine neoplasia (MEN II).

Key words: Pheochromocytoma Crisis – Multiple endocrine neoplasia type II A – Multiple organ failure – Fever – Pulmonary edema – Coma

Pheochromocytoma, a rare neuroendocrine tumor, predominantly presents with hypertension, palpitations, tachycardia and sweating as a result of excessive catecholamine excretion [1–3]. We report the case of a 65 years old women with intermittent hypotension, fever, pulmonary edema, and coma as main presentations of pheochromocytoma or multiple endocrine neoplasia type II A.

Case report

This 65-year-old lady was admitted to our hospital because of fever, dyspnea NYHA IV, retrosternal pain, vomiting and diffuse arthralgia.

The personal history revealed a slightly elevated blood pressure at the age of 62, when varicose veins had been treated. Blood pressure was not followed and no antihypertensive treatment was instituted. She underwent polypectomy in the colon when she was 61-years-old. An abdominal ultrasound examination 4 years before admission had been normal. Three months prior to this hospitalization arthralgia of shoulders, elbow and hands began to appear and improved little with allopurinol and diclofenac.

On admission temperature was 39.5 °C, respiratory rate was 40/min, pulse rate was regular at 130/min, and blood pressure was 120/80 mmHg. The skin in the periphery was cold and blanched, the back was covered with an erythema. The cardiac examination revealed a 3/6 aortic systolic murmur and no hepatojugular reflux. Over the entire lung pulmonary rales were heard. The abdominal examination was unrevealing. On neurological examination the patient was alert and fully oriented. The only abnormality consisted of a delayed light reaction of the pupils and symmetrical mydriasis.

The chest X-ray showed bilateral diffuse infiltration (Fig. 1), compatible with lung edema and the ECG slight disturbances of repolarisation. A general hypokinesia of a slightly dilated left ventricle was noted on echocardiography whereas an abdominal ultrasound revealed normal findings. There was diffuse meteorism on an abdominal X-ray examination.

The initial laboratory workup yielded the following results: sedimentation rate 51 mm/h, hemoglobin 170 g/l, hematocrit 53%, neutrophil count 13700/µl, band forms 16%, lymphocytes 16%, thrombocyte count 446000/µl, blood glucose 19.1 mmol/l, serum sodium 145, potassium 5.1, calcium 2.06 mmol/l, serum creatinine 129 nmol/l (normal 53–97), bilirubin 15 µmol/l, aspartate aminotransferases 40 IU (<20), alanine aminotransferases 31 (<25) IU, alkaline phosphatase 237 IU (6–200), amylase 141 U/l (<120), creatine phosphokinase 191 U/l (<70), MB-fraction 101 U/l, albumin 51 g/l, prothrombin time 65%, fibrinogen level 2.0 g/l, fibrin split products 265 ng/ml (<10); arterial blood gases: pH 6.98, PCO_2 6.1 kPa, PO_2 8.8 kPa, bicarbonate 10.7 mmol/l, base excess −21.8 on nasal oxygen 8 l/min.

The urine contained over 40 erythrocytes per visual field, protein, waxy casts and showed a sodium concentration of 80 mmol/l.

Two hours after admission mechanical ventilation was started for respiratory failure and excessive tachypnoea. By 24 h later blood gases and pH had returned to normal. Mechanical ventilation was continued for 19 days, which necessitated tracheostomy because of clouding of consciousness.

Arterial blood pressure initially was normal. With mechanical ventilation the pressure dropped to 68/30 mmHg, then rose again with i.v. fluids. Cardiac output was low at 2.5 l/min (thermodilution technique); right atrial pressure (10 mmHg) and the pulmonary capillary wedge pressure (13 mmHg) were slightly elevated under mechanical ventilation at 0 mmHg PEEP. Dopamine and i.v. nitroglycerin resulted in a slow hemodynamic improvement. After withdrawal of i.v. catecholamine the mean blood pressure rose intermittently to a maximum of 180 mmHg. Periods with hypotension still occurred. As an example of the fluctuating blood pressure and heart rate see Fig. 2 with data from day 8 and 9. Nitroprusside, phentolamine and propanolol were used to lower blood pressure. On day 8 a hypertensive crisis developed and the patient was successfully defibrillated 14 times for ventricular tachycardia and fibrillation. Intermittent atrial flutter and fibrillation was also observed. Creatine phosphokinase moderately increased with a maximum of 685 U/l (<70). The MB-fraction decreased at the same time from 101 U/l (Day 1) to 36 U/l and stayed below 6% of total CK. The ECG

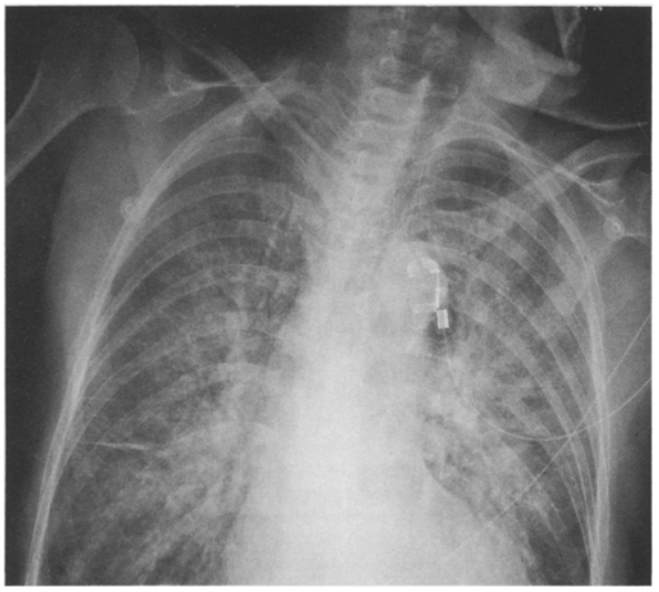

Fig. 1. Chest X-ray on the day of admission showing diffuse bilateral pulmonary edema

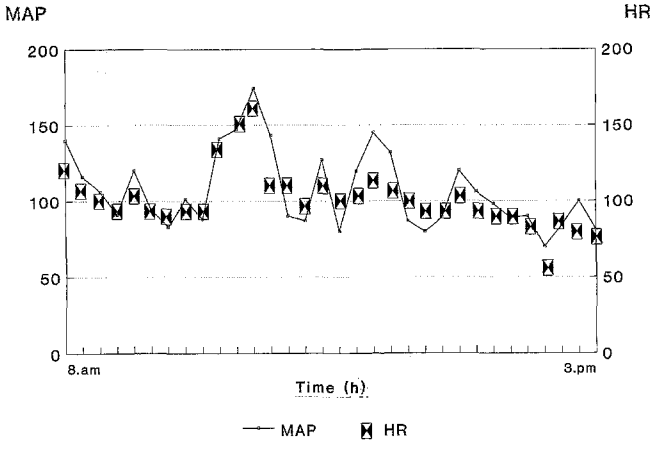

Fig. 2. Mean arterial blood pressure (*MAP*) and heart rate (*HR*) moved in parallel reflecting the effect of catecholamine excess. The data were collected during day 8 and 9

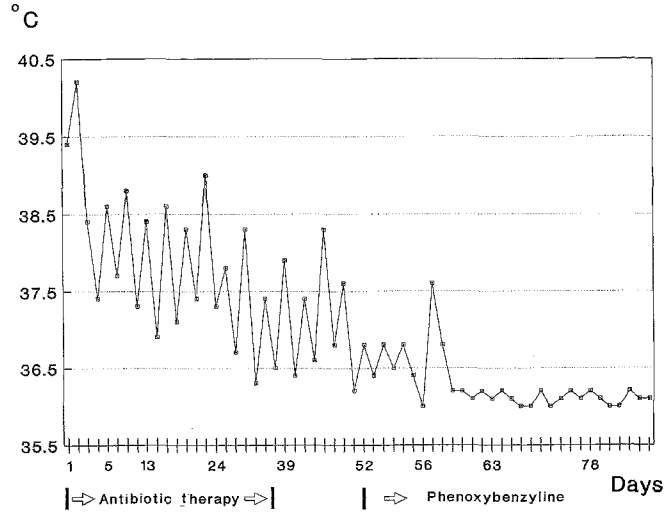

Fig. 3. The initial fever was little influenced by antibiotic treatment. Phenoxybenzyline resulted in normalization of body temperature

series showed inconsistent loss of anteroseptal R-wave and incomplete RBBB.

The high fever continued and was little influenced by antibiotic treatment with amoxicillin/clavulanic acid, gentamycin, ceftriaxone (Fig. 3). The leukocyte count rose to 24000/µl with 40% band forms together with elevated fibrin split products, thrombocytopenia at a minimum of 60000/µl and a low prothrombin time of 19%. Disseminated intravascular coagulation was assumed. On multiple examinations (e.g. pleura, blood, urine, stool, tracheal secretion, catheters, maxillary sinuses) no bacterial growth was detected at the beginning. Nosocomial *Pseudomonas aeruginosa* was cultured after one week of intensive care. Hemodialysis was necessary during 7 days for acute renal failure. Excessive increases in aminotransferases (aspartate 3490, alanine 1813 IU), lactate dehydrogenase (8070 IU), elevated serum amylase (548 IU), bilirubin 195 µmol/l (direct 183 µmol/l) and elevated ammonia (152 µmol/l, normal 12–45), reflected liver and pancreatic damage. Prothrombin time fell to 19%, factor V to 21%. Serological examinations for virus hepatitis remained negative. Bloody diarrhea developed and was negative for clostridium difficile toxin.

The erythema of the back developed into a generalized exanthema which 10 days later resolved with scaling of hands and feet.

A comatose state persisted from day 2 to day 14 and was accompanied by loss of muscle tone in the extremities, unresponsive to painful stimuli. Cerebrospinal fluid was normal. A small ischemic lesion in the right frontoparietal region on the CT-Scan as well as the EEG with diffuse general changes did not explain the coma. Acoustic evoked potential testing yielded normal responses. Flumazenil i.v., a benzodiazepine antagonist only minimally affected the patients state of coma.

After 25 days the patient had slowly recovered from the still unknown disease. She was again oriented and cooperative and later able to stand up for short periods. She was transfered from the ICU to the general ward. The cause for the multiple organ failure had not yet been determined.

Fever, palpitations and hyperkinetic cardiac activity persisted. Pheochromocytma entered the differential diagnosis. A 24 h-urine analysis yielded excessively elevated catecholamine concentrations (adrenaline 483 nmol/d, noradrenaline 1165 nmol/d, vanillylmandelic acid 91 mcmol/d, metanephrine 33645, Normetanephrine 7612, 3-methoxy tyramine of 3051 and dopamine of 2398 nmol/d). Plasma adrenaline supine/standing were 1298/3162 and noradrenaline 2415/5303 pg/ml on day 3 with beta blockade.

A CT of the abdomen revealed a tumor in the left adrenal gland of 4 cm in diameter which was confirmed by MRI. An I-131-benzylguanidine scintigram showed activity only in the left adrenal gland.

After pre-operative treatment with phenoxybenzyline over 3 weeks a pheochromocytoma of the left adrenal gland was removed. Histologically there was invasion into periadrenal fatty and fibrous tissue, tumor tissue necrosis and elevated mitotic activity indicative of malignancy. A biopsy of the right adrenal gland was compatible with adenoma.

The patient recovered well. The urine catecholamine levels were now normal and the I-131-benzyl guanidine scan negative. But high normal calcitonin blood levels (93 pg/ml, normal <100) prompted repeated pentagastrin stimulation. The results were unequivocal. Calcitonin levels were pretest 354 pg/ml, under stimulation over 2000 pg/ml, confirming the suspicion of thyroid tumor. During a second operation a multicentric medullary thyroid carcinoma was removed. Carcinoma tissue was found in 1 of 22 lymph nodes.

The patients family consists of 54 members of whom 46 responded to a questionnaire and returned a 24 h-urinary collection for catecholamine analysis. A brother of 80 years and a niece have had proven pheochromocytoma. The niece also has a medullary thyroid carcinoma. All other living members of the family showed no abnormality in 24 h-urine catecholamine analysis and no symptoms of pheochromocytoma in the questionnaire.

Discussion

Pheochromocytoma is a rare cause of arterial hypertension [4]. In 20% it is part of the multiple endocrine

neoplasia syndrome type II including adenomas of the thyroid gland [5]. The majority of patients report headache, sweating, palpitations and pallor. Other less frequent symptoms are nervousness, tremor, nausea, fatigue, acute abdominal pain, visual disturbances, weight loss and dyspnea [3].

The case of this 65-year-old woman with pheochromocytoma is exceptional. She revealed none of the abovementioned major symptoms. Excessive catecholamine excretion manifested itself with acute fever, lung edema, circulatory shock, multiple organ failure and coma. "Pheochromocytoma crisis" has been proposed for this condition by some authors [3, 7–9].

Acute dyspnea reflected bilateral lung edema and mechanical ventilation had to be instituted 2 h after admission. However high normal capillary wedge pressure was compatible with ARDS rather than cardiac edema. It has been hypothesized by others, that a pulmonary capillary leak is caused by the toxic effect of catecholamine excess. Zimmermann et al. have observed several episodes of lung edema in 2 patients with pheochromocytoma during hemodynamic monitoring before and during removal of pheocromocytoma [10]. They were able to rule out cardiac failure as a cause. In animal experiments high dose catecholamine infusions have resulted in non-cardiac lung edema [11].

On admission arterial pressure was within normal limits at a pulse rate of 130/min. Cold extremities reflected centralisation of the circulation. Mechanical ventilation instituted 2 h after admission resulted in hypotension (arterial pressure 66/30 mmHg) unmasking hypovolemia. Hypovolemia is a well known sign of pheochromocytoma [12].

After 3 days severe hypertension developed showing a characteristically labile behavior. Blood pressure could change from one minute to the other. Figure 2 shows the overplay of baroreceptor regulation: blood pressure and heart rate rose and fell in parallel.

Depressed myocardial contractility resulted in a low cardiac output of 2.5 l/min at high normal filling pressures. Myocardial damage due to catecholamine excess was likely to be responsible for later ventricular tachycardia degenerating into fibrillation. Repeated electrical defibrillation was necessary. Typically severe hypertension had occurred minutes before the serious arrhythmias. No consistent evidence for myocardial infarction was found. ECG showed intermittend loss of R-waves anteroseptally and incomplete right bundle branch block. Van Vliet has examined 26 fatal cases of pheochromocytoma [13]; 15 showed histological evidence of "active catecholamine myocarditis": focal degeneration and necrosis of myocardial cells, inflammatory cells, diffuse edema and left ventricular hypertrophy. Atrial and ventricular arrhythmias had been common in these patients.

Our patient had to undergo dialysis for renal failure. The urinary analysis showed evidence of tubular necrosis which is compatible with ischemic damage to the kidney from catecholamine excess. Again hypovolemia may have contributed to the renal dysfunction.

Liver damage was documented with a low prothrombin time, low factor V concentration, metabolic acidosis, elevated aminotransferase levels, and elevated ammonia and bilirubin concentrations. In combination with bloody diarrhea and an elevated serum amylase these findings probably reflect diffuse ischemic damage to liver, pancreas and the gut. It is conseivable that catecholamine excess results in vasospasm. Some degree of disseminated intravascular coagulation may have contributed, but the minimal thrombocyte count of 60000/μl makes this mechanism less likely. Low cardiac output with hypoperfusion could also have had detrimental effects.

Multiple organ failure caused by pheochromocytoma again is a rare condition. Newell has summarized 5 patients, 2 from his own series, who showed variably arterial hypo-/hypertension, encephalopathy, renal insufficiency and respiratory failure [7].

Fever has been reported by several authors as a feature of pheochromocytoma [7, 9, 14]. Our patient had an elevated temperature over 3–4 weeks, which fell into normal range only after the institution of phenoxybenzyline therapy (see Fig. 3). No evidence for an infection was found during the first week of the acute illness. Later a nosocomial infection with *Pseudomonas aeruginosa* could have contributed to the fever.

The diffuse erythema and later scaling of hands and feet pointed to toxic shock syndrome. But staphylococcal antitoxin antibody could not be demonstrated. We have not found erythema described as a sign of pheochromocytoma in the literature.

Coma is a rare consequence of pheochromocytoma. In our patient it developed on the second day of hospitalization and was accompanied by total loss of muscle tone in the extremities. EEG, CT and normal cerebrospinal fluid examinations were compatible with diffuse encephalopathy. Hepatic failure may have contributed to the cerebral dysfunction. But the coma persisted while ammonia levels fell close to the normal range. The full mental and neurological recovery from coma and loss of muscle tone in this patient rules out major ischemic or hemorrhagic vascular events. Disseminated intravascular coagulation with typical multiple cerebral hemorrhages had been found by Hill et al. in 1 patient who died from a pheochromocytoma [8]. In addition a thrombotic occlusion of the right middle cerebral artery had been found. A further case of pheochromocytoma had also shown transient unconsciousness [9]. CT scan had revealed bilateral cerebellar infarction. Cerebral artery spasm, embolism, intravascular thrombosis and disseminated intravascular coagulation have been discussed as possible pathogenetic mechanisms for cerebral dysfunction in pheochromocytoma. Hypertensive encephalopathy was probably not the cause of coma in our patient. In one case of MEN II coma had been more likely due to hypoglycemia from insulinoma than the result of catecholamine excess [14].

In summary this 65-year-old woman was treated 25 days on the intensive care unit for coma, circulatory shock, repeated ventricular fibrillation during periods of severe hypertension, respiratory and renal failure, dissem-

inated intravascular coagulation and liver dysfunction. With phenoxybenzyline the fever disappeared. The patient is doing well 23 months after surgical removal of a pheochromocytoma and a thyroid carcinoma.

The case demonstrates, that multiple organ failure and coma may be caused by previously oligo- or asymptomatic pheochromocytoma. Pheochromocytoma should be considered in patients with shock, fever and multiple organ failure of unknown origin. The observation of myocardial insufficiency, intermittent hypertension and arrhythmias renders excess catecholamine excretion even more likely. The diagnosis of this rare condition was rewarding in this case as the disease was fully reversible by surgical removal of the pheochromocytoma.

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