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A case of central alveolar hypoventilation in medullary thyroid cancer

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Some two thirds of patients with medullary thyroid carcinoma (MTC) die of the tumour, principally as a result of local complications [1]. We report the first case of a 68-year-old woman with sporadic bilateral MTC who experienced near death due to central alveolar hypoventilation (CAH) which we suspect to be an anti-Ri antibody-mediated paraneoplastic expression.

Six years previously the patient had undergone near total thyroidectomy and lymphadenectomy for sporadic bilateral MTC stage III. Postoperatively calcitonin (853 pmol/l; nv <10) indicated probable residual tumoral tissue. The patient was placed on therapy with laevothyroxine and was checked for euthyroidism every six months by means of TSH and free T_4. Two years later she for the first time experienced progressive gait difficulty associated with exertional dyspnoea.

She was admitted for progressive disabling gait ataxia and exertional dyspnoea of NYHA class III. The current medication was candesartan 8 mg for mild arterial hypertension and laevothyroxine 0.1 mg. Neurological examination revealed ocular saccades (opsoclonus), cerebellar ataxia and peripheral polyneuropathy in the four limbs. Arterial blood gas analysis showed chronic global respiratory insufficiency (pH 7.32, pCO_2 9.6 kPa, pO_2 6.0 kPa, bicarbonate 38 mmol/l, SaO_2 74%). The admission laboratory values including thyroid hormones (TSH 2.42 mU/L [nv: 0.27–4.2] and free T_4 14.6 pmol/L [nv: 12–22]) were normal except for calcitonin (1116 pmol/l). A few days later she presented sudden, near fatal respiratory arrest. Transferred to the ICU for non-invasive mechanical ventilation, she improved rapidly. Further diagnostic procedures targeting cardiac, pulmonary or muscular causes of chronic alveolar hypoventilation (ECG, echocardiography, complete lung function test, thoracic CT scan, electromyography), were normal. Abdominal CT scan and mammography were unremarkable. Cerebral MRI showed cerebellar atrophy and the cerebrospinal fluid findings were normal. Further immunological investigations revealed a positive immunofluorescence test for anti-Ri antibodies. In contrast, voltage gated calcium channel antibodies, anti-acetylcholine receptor antibodies and anti-myelin associated glycoprotein (IgM) antibodies were normal. Immuno-electrophoresis of the urine showed paraproteins of Bence Jones kappa type (13.3 mg/l; nv <7.1). Monoclonal gammopathy of undetermined significance (MGUS) was presumed, given the normal bone marrow findings. Although whole body scintigraphy with ^{111}In-octreoid failed to show recurrence of MCT, a partial body ^{18}F-FDG PET-CT scan first and MRI of the neck thereafter revealed bilateral MTC recurrence. Histology of the tissue obtained by selective bilateral neck dissection showed level II–IV tumour cells in the remaining thyroid gland and in 10 of 61 excised lymph nodes. In conclusion, the findings in our patient with incomplete MTC resection six years before suggest paraneoplastic involvement of the peripheral and central nervous system which is characterised clinically by peripheral polyneuropathy, cerebellar ataxia, opsoclonus and central alveolar hy-poventilation. The patient was discharged after surgery. Alveolar hypoventilation im-proved markedly with nocturnal nasal nonin-vasive bilevel positive airway pressure venti-lation. During 18 months' follow-up no epi-sodes of respiratory arrest recurred.

While neuropathy is frequently associated with MGUS [2], involvement of the central nervous system, as observed in our patient, is rare. Thus, tremor and signs of pyramidal system involvement have been described in a few patients with monoclonal (IgM-k, IgA-k, IgG-k) and polyclonal (IgG, IgM) gammopathy [3].

On the other hand, paraneoplastic cerebellar and brainstem involvement has been reported to be associated with anti-Ri antibodies in breast cancer, small cell lung cancer, bladder cancer and thymic carcinoma [4]. As far as we know this is the first case of MTC with anti-Ri antibody-associated cerebellar ataxia and CAH. It is likely that anti-Ri anti-bodies, which inhibit the interaction between Nova-1 (a neuron-specific RNA-binding pro-tein) and RNA, are responsible for the neu-rological symptoms observed [5]. CAH has al-ready been reported in a patient with occult small cell carcinoma of the lung, but it was associated with paraneoplastic brainstem encephalitis [6]. Since only two-thirds of patients with MCT die of local or metastatic tumour complications, we suspect that central alveolar hypoventilation-associated respiratory failure may be one cause of death in the others.

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