

## Peer reviewed article

## Spontaneous leg haematoma in a patient anticoagulated with nadroparin for suspected pulmonary thromboembolism

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Fixed-dose, subcutaneous Low Molecular Weight Heparin (LMWH) is as effective and safe as adjusted-dose, intravenous unfractionated heparin (UFH) for the initial management of venous thromboembolism and symptomatic pulmonary thromboembolism [1-4]. Clinical experiences indicate that bleeding is a major side effect, not only of UFH, but also of LMWH [5].

An 81-year-old woman (60 kg) was admitted with a clinically suspected pulmonary embolism (SPE) with a 2-day history of pleuritic chest pain and dyspnoea. Her past medical history showed congestive heart failure, atrial fibrillation (AF) and hyperthyroidism, immobilisation due to femoral head fracture 7 years previously. Propylthiouracil, coumadin, aspirin, perindopril, spironolactone, and digoxin were started in May 2000 and propylthiouracil and coumadin was discontinued after 3 months follow-up. Owing both to SPE and chronic AF she was started on nadroparin subcutaneously twice daily 5700 UI AXa/0.6 ml. The ventilation/perfusion scan of the lung was reported as having low probability of pulmonary embolism and a duplex ultrasound of the lower limbs was negative for DVT the night after the symptoms started. Despite these findings anticoagulant treatment was continued due to the chronic AF. Except for slightly raised white blood cells and a raised creatinine on admission her laboratory results and coagulation parameters were within normal limits. Two days after anticoagulant treatment, she complained of sudden onset of left leg pain with the finding of a tender haematoma (measuring 5×10×25 cm). There was no history of trauma. Together with nadroparin aspirin was also discontinued.

Initially she was managed conservatively, nonetheless the haematoma progressed further over 8 days. Immediate surgical intervention was considered applicable owing to severe systemic co-morbidity of the patient. Subsequently, however, the significant increase in dimensions of the haematoma and accompanying risk of impairment in the vascular supply of the extremity was accepted

as the indication for surgery. General anaesthesia was preferred. Surgical exploration revealed 600 ml of organised clot located in the anterolateral compartment of the proximal 1/3 of the leg. Sudden death of unknown cause was observed two days after operation. Anti Xa determination was not carried out at the time of the clinical event due to a lack of laboratory facilities. No autopsy was performed due to family refusal.

Bleeding is the most important side effect of LMWH therapy. LMWHs, including nadroparin, have been shown in multiple studies to be associated with some haemorrhagic complications (spontaneous suprachoroidal bleeding, subcutaneous haematoma, intrahepatic haemorrhage, psoas haematoma after lumbar plexus block and an increase in the incidence of postoperative intracranial haemorrhage in patients treated prophylactically for deep venous thrombosis (DVT) being operated on for brain tumours) [6]. Subcutaneous haematoma, wound and injection site haematoma are relatively common adverse effects of therapy with LMWH including nadroparin [7].

The bleeding due to LMWHs seems to be effected by age of patients, concomitant use of medicines, side effects of LMWH itself, dose given, renal function and additional medical problems.

In clinical trials conducted in older patients (mean age usually >60 years), nadroparin was at least as effective and even more safe as UFH in preventing DVT and pulmonary embolism after major general or orthopaedic surgery, and in bedridden patients [8]. The frequency of major bleeding was similar in the prophylaxis of DVT in patients undergoing general surgery with nadroparin in three different studies (0.4, 4.9 and 5.3 percent, respectively) [9].

The concomitant use of medicines affects haemostasis, such as non-steroidal anti-inflammatory drugs (ibuprofen, ketorolac and aspirin), platelet inhibitors or other anticoagulants.

Heparin-induced thrombocytopenia (HIT) is a severe adverse effect of heparin therapy. Although most cases occur in patients receiving unfractionated heparin, HIT can arise in venous thrombosis prophylaxis with nadroparin [10]. In this particular patient no thrombocytopenia was observed as a predisposing factor for this complication.

They et al. performed a dose ranging study with nadroparin and compared the results with a regimen of dose adjusted UFH. The highest doses (5700 to 9500) resulted in an unacceptable high rate of bleeding complication. No major bleeding was observed in the lowest dose (1900 to 3800 IU) [11]. In another prospective study no bleeding events occurred in the patients given the lower dose compared with two major haemorrhages in those given the higher dose. According to both studies the risk of bleeding complications with LMWH is dose dependent [12].

In a study a significant accumulation of the anti-factor Xa activity was observed in the healthy elderly and in the patients but not in the healthy young subjects. There was also significant correlation between the clearance of creatinine and the clearance of the anti-factor Xa activity. Together with ageing, the low creatinine clearance of our case might have caused a significant accumulation of the anti-factor Xa activity [13].

Even if anti Xa determination and autopsy are lacking in our case the haematoma should most probably be regarded as a complication of nadroparin as it arose 2 days after use of nadroparin, and the other coagulation parameters were normal at the time of event.

A complication of this type offers new evidence on the safety hazards in the treatment and prevention of thromboembolism in elderly patients.

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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<sub>4</sub>. 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<sub>2</sub> 9.6 kPa, pO<sub>2</sub> 6.0 kPa, bicarbonate 38 mmol/l, SaO<sub>2</sub> 74%). The admission laboratory values including thyroid hormones (TSH 2.42 mU/L [nv: 0.27-4.2] and free T<sub>4</sub> 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 <sup>111</sup>In-octreoid failed to show recurrence of MCT, a partial body <sup>18</sup>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 hypoventilation. The patient was discharged after surgery. Alveolar hypoventilation improved markedly with nocturnal nasal noninvasive bilevel positive airway pressure ventilation. During 18 months' follow-up no episodes 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 antibodies, which inhibit the interaction between Nova-1 (a neuron-specific RNA-binding protein) and RNA, are responsible for the neurological symptoms observed [5]. CAH has already 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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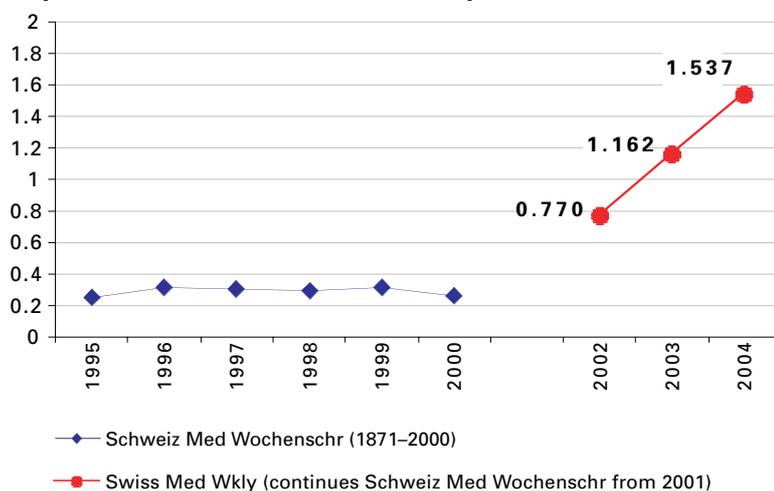
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