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Case report

Acute quadriplegic myopathy following autologous peripheral blood stem cell transplantation for breast cancer

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Summary:

Autologous peripheral blood stem cell transplantation (APSCT) is increasingly used in the treatment of breast cancer. We report a patient who experienced septic shock, and after treatment with antibiotics, high-dose corticosteroids and mechanical ventilation due to respiratory insufficiency, developed quadriplegia. Electroneurophysiological examination, as well as a muscle biopsy, showed a typical picture of acute quadriplegic myopathy with loss of thick filament proteins. This is, to the best of our knowledge, the first reported case of this complication following APSCT.

Keywords: autologous stem cell transplantation; breast cancer; myopathy; myosin; steroids

During recent years, breast cancer has become the most common indication for autologous transplantation in the United States, and with the introduction of autologous peripheral blood stem cell transplantation (APSCT) transplant-related mortality has markedly diminished.[1] However, serious complications causing prolonged morbidity can still occur. We report a patient who developed acute quadriplegic myopathy (AQM) after APSCT for breast cancer. In intensive care unit (ICU) patients, AQM is an underestimated syndrome. It is an important cause of morbidity in the ICU, and it has an economic impact with significant consequences on ICU and hospital resource utilization.[2–4] High-dose corticosteroid treatment in combination with non-depolarizing neuromuscular blocking agents and severe systemic illness appear to be the main risk factors associated with AQM.[5]

Case report

A 52-year-old woman presented in November 1996 with a lump in her left breast, and fine needle aspiration showed malignant cells. She underwent partial mastectomy, and a 14 mm poorly differentiated ductal cancer was found with metastases in 13/15 axillary lymph nodes. She was entered in a Scandinavian multicenter trial (SBG 9401) that randomized patients to either dose-escalated courses of 5-fluorouracil, epirubicin and cyclophosphamide (FEC), or FEC followed by APSCT. The patient was admitted in March 1997 to undergo APSCT after conditioning with the STAMP protocol including carboplatin, cyclophosphamide and thiothepa. Her previous medical history was unremarkable, except for an insignificant atrial septal defect and short episodes of atrial fibrillation. Prophylactic treatment with acyclovir and fluconazole was given. Conditioning was uneventful except for some nausea and vomiting, and short periods of atrial fibrillation not requiring medication. The protocol included G-CSF 5 μg/kg/day from day 1 post-transplant. Four days after reinfusion of her stem cells (day 4), the patient was neutropenic (ANC $<0.1 \times 10^9$/l) and developed fever, 39°C, tachycardia and hypotension. This clinical picture of septic shock did not improve despite initiation of treatment with imipenem-cilastin and intensified i.v. hydration. The patient was therefore admitted to the ICU. On admission to the ICU she had a fever of 40°C, tachypnoea, an arterial oxygen saturation of 70% and a systolic blood pressure of 60 mmHg. She was treated with epinephrine, phenylephrine, dopamine, and oxygen supplementation by continuous positive airway pressure by face mask (CPAP level 5–7 cm H_2O). Her clinical status improved initially. Blood cultures obtained at the onset of fever showed growth of *Streptococcus mitis* sensitive to imipenem-cilastin. Chest X-ray revealed bilateral infiltrates suggestive of impending adult respiratory distress syndrome, and therefore treatment with corticosteroids, hydrocortisone 800 mg/day, was initiated.[6] Despite continued treatment as described, her status deteriorated on day 5, with impaired oxygen saturation and carbon dioxide retention necessitating oro-tracheal intubation and mechanical ventilation. For intubation the patient received 50 mg of succinylcholine chloride i.v. No other muscle relaxants were used during her ICU stay. Despite an inspired oxygen fraction of 0.6 and end-expiratory pressure of 8 cm H_2O, arterial oxygenation remained inadequate. A desicision was made on day 6 to try and improve oxygenation by inhalation of nitric oxide (NO). The patient responded to stepwise increases of the NO concentration with a maximum response of 10 PPM of NO. On intubation, minor bleeding from the trachea was noticed. A new chest X-ray showed increasing infiltrates,

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and erythromycin and ganciclovir were added to provide better cover against other possible infectious agents. An immunofluorescence assay of a sputum sample was negative for *Pneumocystis carinii*. Over the ensuing days her clinical status remained unchanged with fever between 39 and 40°C, but repeated cultures from blood, urine and airways were all negative. Empirical therapy with liposomal amphotericin B (AmBisome 100 mg/day) was added on day 9. The patient required daily erythrocyte and platelet transfusions and had persistent minor bleeding from the tracheal tube. Periods of atrial fibrillation were treated with digoxin and sotalol. Although she had been ventilated by a pressure-controlled mode of mechanical ventilation never exceeding an airway pressure of 28 cm H_2O, on day 9 minor subcutaneous and mediastinal emphysema was detected. The subcutaneous emphysema subsequently increased, covering the whole trunk, and she also had a pneumoperitoneum. No pneumothorax was found on chest X-ray which also showed clearing of the pulmonary infiltrates. Treatment included only a reduction of airway pressure to a maximum of 20 cm H_2O and increased ventilator rate. The neutrophil count was now 1.9×10^9/l and she was almost afebrile. Over the ensuing days, her clinical status and chest X-ray gradually improved. Treatment with NO was stopped on day 13. However, when sedation was withdrawn on day 14 complete paralysis of both the upper and lower extremities was discovered. Neurological examination showed complete paralysis with absent deep-tendon reflexes, but intact cutaneous sensation as well as a normal cranial nerve status and normal eye movement. CT scan of the brain was normal; a lumbar puncture was not performed due to continued profound thrombocytopenia. AQM was suspected and treatment with corticosteroids that had been given from day 5, was discontinued. An electroneurophysical examination (EMG and nerve conduction studies) on day 17 was inconclusive, suggesting both peripheral nerve and muscle involvement. However, a further examination on day 23 demonstrated normal motor and sensory nerve conduction velocities, low or absent compound muscle action potentials and sensory action potential amplitudes which were lower than normal. On day 23, voluntary recruited short duration and low amplitude myopathic motor unit potentials were recorded in one distal lower extremity muscle, but no voluntary activation was observed in any of the other proximal and distal lower and upper extremity muscles examined by concentric needle EMG. An increased amount of spontaneous EMG activity (high frequency repetitive discharges, fibrillation potentials and positive sharp waves) was observed in proximal and distal upper extremity muscles. A biopsy sample from m. tibialis anterior was taken on day 17. Frozen sections stained for hematoxylin–eosin showed an increased variation in muscle fiber size. The large majority of muscle fibers showed only weak reactivity with enzyme-histochemical myofibrillar ATPase staining. Lysosomal proteolysis was not significantly activated, according to acid phosphatase stains and only a small number of both atrophic and normal size muscle fibers showed increased Leu-19 immunoreactivity, indicating ongoing muscle fiber regeneration or peripheral denervation. Electrophoretic separation of myofibrillar proteins by sensitive silver stained 12% SDS-PAGE showed a preferential loss of myosin and myosin-associated thick-filament proteins (Figure 1).

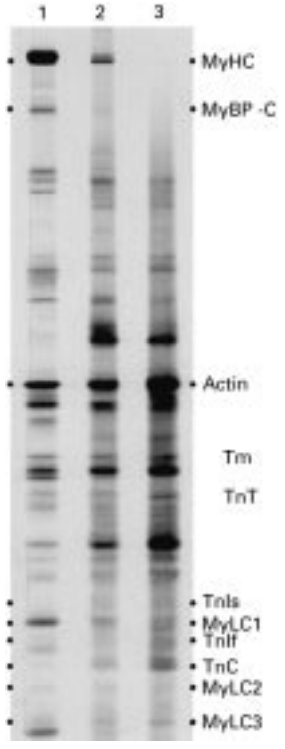

Figure 1 Expression of thick and thin filaments in whole-muscle biopsy cross-section. Electrophoretic separation of thick- and thin-filament protein isoforms from 10 μm cross-sections of muscle biopsies by 12% SDS-PAGE from a normal control (lane 1), an AQM patient with partial loss of myosin and myosin-associated proteins (lane 2), and our patient on day 17 after APSCT (lane 3). Protein contents adjusted so that the actin contents are almost identical between patient and control. Thick-filament proteins (myosin heavy chain, MyHC, myosin binding protein C, MyBP-C, and myosin light chain, MyLC, isoforms) are indicated together with thin filament proteins (actin, tropomycin, Tm, and different troponin, Tn, isoforms).

Although she was still grossly paraplegic, weaning from mechanical ventilation was started on day 17 and the patient was extubated on day 20. She was discharged from the ICU on day 30. At this time, she had regained some muscle strength and was able to move her feet, her hands and some of her fingers. By day 52 she could swallow liquids and eat food, she could sit up for short periods of time without the support of another person, and could stand up with the support of two members of the staff. She was transferred to a rehabilitation unit, and with physical therapy her condition rapidly improved. She returned to her home on day 94, by which time she was able to walk with the aid of a walking stick. Three months later, ie 6 months after her transplant, she had made a full recovery except for paresis of three toes of her right foot. She has been treated with local radiation to the chest wall and regional lymph nodes (46 Gy), as part of the protocol. At the present time (June 1998) she has no signs of local recurrence or distant metastases.

Discussion

Acute generalized muscle weakness in critically ill patients acquired within the ICU has received increasing interest

during the past two decades. Acute polyneuropathies, such as the Guillain–Barré syndrome and acute sensorimotor polyneuropathy (critical illness neuropathy), have frequently been reported as a common cause of weakness in patients in the ICU, and have been described after bone marrow transplantation.[7,8] The normal motor and sensory conduction velocities in this patient exclude a demyelinating polyneuropathy. The low or absent compound muscle action potentials upon supramaximal stimulation of the motor nerves indicate a preferential motor axonopathy. The sensory action potentials which are slightly lower than normal in the patient are interpreted as being due to the unfavorable recording conditions in the ICU. However, analysis of the muscle biopsy specimen showed myopathic alterations and a preferential loss of myosin and myosin-associated thick-filament proteins, ie findings not observed in acute polyneuropathies.

The acute quadriplegic myopathy in ICU patients, originally reported by MacFarlane and Rosenthal in 1977,[9] was initially regarded as a rare event of limited clinical significance. However, recent prospective and retrospective studies have shown that this is an under-appreciated entity, which is a significant source of morbidity in the ICU, and has significant economic consequences on the usage of health resources.[2–4] There is compelling evidence that this syndrome is associated with altered muscle membrane properties and selective loss of myosin and myosin-associated proteins. The altered membrane properties are most probably the primary cause of the absent or very low compound muscle action potentials and the increased amount of spontaneous EMG activity. The loss of thick filament proteins appears to be caused by a block in protein synthesis at the transcriptional level and enhanced myofibrillar protein degradation.[10] High-dose corticosteroid treatment in combination with non-depolarizing neuromuscular blocking agents and severe systemic illness appear to be the main risk factors associated with AQM.[5] It should be pointed out that, except for one dose of succinylcholine chloride before intubation, our patient did not receive therapy with muscle relaxants, demonstrating that steroid treatment and severe illness alone can induce AQM. Muscle biopsy analyses are essential in the diagnosis, since clinical observations and electrophysiological findings are not conclusive. Muscle biopsy analyses in our patient showed findings consistent with AQM, ie myopathic alterations, focal or diffuse loss of myofibrillar ATPase activity and a preferential loss of myosin and myosin-associated proteins.

AQM has previously been described after organ transplantation, mainly in patients who have undergone liver or lung transplantation.[11] A search of the literature (MEDLINE) failed to reveal any previously published cases of this complication in the setting of stem cell transplantation. Two patients with acute myopathy have been reported as part of a clinical syndrome associated with carboplatin toxicity.[12] However, these patients also exhibited multiorgan failure with profound renal, cardiac and CNS toxicity, and died as a result of that syndrome. Admittedly, our patient received carboplatin as part of her conditioning regimen, but since her clinical picture was quite different from the patients described above, it is unlikely that carboplatin contributed to the myopathy seen in our patient. Instead, prolonged administration of corticosteroids in combination with systemic illness are more likely to have played a role in the development of the myopathy.

In conclusion, we report (to the best of our knowledge) the first case of AQM after APSCT. This complication should accordingly be kept in mind in the event of acute weakness following APSCT.

Acknowledgements

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