9. Skeletal muscles and malignancy

Dragomir Marisavljevic

Specialist in Internal Medicine, Professor of Internal Medicine-Hematology, Faculty of Medicine
University of Belgrade, Belgrade, Serbia

Abstract. Malignancy can have different impacts on the structure and function of skeletal muscles.

There are only a few of the primary muscle cancer annually with less than one such case per one million inhabitants. The most common malignant tumor arising in muscle is rhabdomyosarcoma. Location, histologic appearance and tumor genetics all impact the likelihood of cure. The secondary malignant involvement of skeletal muscles occurs only in the case of the extensive presence of malignancy, when there are metastases elsewhere.

Systemic influence of malignancy on skeletal muscles can be manifested as neuromuscular paraneoplastic syndrome, with Lambert-Eaton myasthenic syndrome and dermatomyositis/polymyositis as the most common forms. Tumor cachexia and decreasing of skeletal mass with consecutive loss of condition due to bed rest during prolonged treatment of malignant diseases are also consequences of systemic influence of malignancy on skeletal muscles. In such cases nutritional support and medical rehabilitation are useful therapeutic measures.
Medications are one of the most common causes of diseases of skeletal muscles. The severity of drug-induced myopathies range from mild myalgias with or without weakness, up to severe myopathy with very pronounced muscle weakness and massive rhabdomyolysis with acute renal failure.

**Agenda**

1. Skeletal muscles malignancies
2. Systemic influence of malignancy on skeletal muscles changes
3. Influence of malignancy treatment on skeletal muscles changes

**1. Skeletal muscles malignancies**

**1.1. Primary skeletal muscles malignancies**

A tumor growth in the skeletal muscles is a rare condition, and it will in most cases involve a benign tumor. There are only a few of the malignant tumors (muscle cancer) annually with less than one such case per one million inhabitants. The tumor arises from increased and/or altered growth of muscle cells. Benign tumors are unable to grow into surrounding tissues or spread with blood, but malignant tumors do have this ability. Since muscles have a large blood supply, malignant tumors tend to spread rapidly, and it is therefore a very serious disease with high mortality. The most common tumors arising in muscle are soft tissue sarcomas, fibromatoses, and hemangiomas (1).

**Symptoms**

Symptoms of benign and malignant muscle tumors are different. Although both types of tumors can be felt in the muscle as a lump, benign tumors will usually not be tender and will grow relatively slowly. It can be pushed freely (shifted) under the skin and the connective tissue (displaceable). The malignant tumors might be tender or not. It might have arisen rather fast due to rapid growth. It might be attached to the skin or to the muscle fascia and it is difficult or impossible to push or shift under the skin (non displaceable).

**Diagnosis**

If there is a suspicion of a tumor, there is a choice of different image diagnostics to establish a diagnosis about the size and possible spread of the
tumor. A biopsy (a tissue sample) will also be performed to determine if the tumor contains malignant cells.

Pathology

Rhabdomyosarcoma (RMS) is a cancer made up of cells that normally develop into skeletal muscles. About 7 weeks into the development of an embryo, cells called rhabdomyoblasts (which will eventually form skeletal muscles) begin to form. These are the cells that can develop into rhabdomyosarcoma. Since this is a cancer of embryonal cells, it is much more common in children, although it does sometimes occur in adults.

Skeletal muscle cancers can start nearly anywhere in the body. Common sites include: head and neck (near the eye, inside the nasal sinuses or throat, or near the spine in the neck), urinary and reproductive organs (bladder, prostate gland, or any of the female organs), arms and legs, and trunk (chest and abdomen).

Rhabdomyosarcoma is the most common soft tissue sarcoma of childhood and adolescence, usually appearing before the age of 20 (over 85%). Interestingly, it occurs most commonly in the head and neck or genitourinary tract, usually at sites where there is little, if any, normal skeletal muscle. This tumor occurs in three different histologic types: embryonal rhabdomyosarcoma (the most common type, usually affects infants and young children, tends to occur in the head and neck area, bladder, vagina, or in or around the prostate and testicles); alveolar rhabdomyosarcoma (typically affects older children or teens and occurs more often in large muscles of the trunk, arms, and legs, tends to grow faster than embryonal type and usually requires more intensive treatment) and anaplastic rhabdomyosarcoma (uncommon type that occurs in adults but is very rare in children). (2)

Chromosomal translocations are found in most cases of the alveolar variant; the more common t(2;13) translocation fuses the PAX3 gene on chromosome 2 with the FKHR gene on chromosome 13. PAX3 functions upstream of genes that control skeletal muscle differentiation, and tumor development probably involves dysregulation of muscle differentiation by the chimeric PAX3-FKHR protein.

Treatment

Rhabdomyosarcomas are aggressive neoplasms treated with a combination of surgery, chemotherapy, and radiation. Surgery to remove the tumor may be difficult or impossible depending on the location of the tumor.
Location, histologic appearance, and tumor genetics all impact the likelihood of cure, with progressively worsening rates for embryonal, anaplastic and alveolar variants, in that order. The malignancy is curable in almost two thirds of children; the prognosis is much less favorable in adults with the anaplastic type. If there is no evidence of metastasis, surgery combined with chemotherapy and radiation offers the best prognosis. Patients whose tumors have not metastasized usually have a good chance for long-term survival, depending on the subtype of the tumor (2).

1.2. Secondary skeletal muscles malignancies

Secondary or metastatic skeletal muscles malignancies are rare (incidence 0.16-0.8%), which can be explained by increased resistance of muscle to malignant process due to production of lactic acid in the muscles which inhibits the growth of tumor cells. In addition, the variation of pressure in the muscle tissue and the presence of protease inhibitors in the extracellular matrix also protect muscle from the invasion of tumor cells (3). Therefore, the secondary malignant involvement of skeletal muscles occurs only in the case of the extensive presence of malignancy, when there are metastases elsewhere. The prognosis of patients with metastases in skeletal muscles is poor. Their survival is short and amounts to an average of 9 months.

In most patients, metastases in skeletal muscles are manifested as 'painful' mass. Although it may be the initial manifestation of primary malignancy, metastases in skeletal muscles usually occur later, and sometimes as a manifestation of disease recurrence (4). The most common tumors which disseminate in muscles are lung tumors and tumors of gastrointestinal tract, and the most common site of metastasis are limbs. In most cases the primary origin of malignant tumors can be determined on the basis of morphological features and immunophenotype of tumor cells. The best imaging method for determining the presence of metastases in skeletal muscles is magnetic resonance (NMR), although NMR findings in metastatic skeletal muscles are often reminiscent of the soft tissue sarcomas. However, in comparison to soft-tissue sarcomas in patients with skeletal metastases the "painful mass" and extensive increase in peritumoral tissues are more often presented.

The treatment depends on the clinical condition of the patient. The treatment may include radiotherapy, chemotherapy and surgery. Wide surgical excision facilitates clinical symptoms and can result in a prolongation of survival. Radiation therapy is also effective in pain control and size of metastatic lesions.
2. Systemic influence of malignancy on skeletal muscles changes

2.1. Tumor cachexia

The patients whose body weight before the diagnosis of malignancy or during its therapy reduces have a worse prognosis. If nothing is done, the end result is a development of cachexia, which is a significant cause of death in 5-25% of patients. The therapeutic approach to this problem is complex in terms of combining high-protein diet, reduced synthesis of positive acute phase reactants and the inclusion of patients in routine rehabilitation program to minimize further loss of fitness and to stimulate postprandial anabolism by physical activity (5).

The cancer results in perturbations in skeletal muscle protein metabolism leading to muscle wasting. Although severe wasting is seen primarily in persons with advanced malignancies, a number of cancer patients show some degree of wasting at presentation. Although the cancer-related skeletal muscle wasting is in part attributable to a decreased muscle protein synthesis, its primary cause appears to be the increased muscle protein degradation. Although several proteolytic systems may be involved, compelling evidence suggests that the major system responsible for skeletal muscle protein degradation in cancer is the ATP-dependent ubiquitin-proteasome system. Other contributing factors include pro-inflammatory cytokines (TNF-α, IL-1, IL-6) and the tumor-released proteolysis-inducing factor. Decreased physical activity and decreased nutritional intake may also play a role. Cancer-related skeletal muscle wasting is clinically significant because of its profound effects on functional outcomes and quality of life. Nevertheless, no specific interventions have proved to be effective in preventing or reversing the problem. Interventions such as nutritional supplementation and appetite stimulants (megestrol acetate, dronabinol) are only partially helpful. A non-pharmacologic intervention that may attenuate cancer-related skeletal muscle wasting is progressive resistance exercise training which is a potent stimulus of growth in muscle mass and strength. Progressive resistance exercise training may attenuate cancer-related skeletal muscle wasting by down regulating the activity of proinflammatory cytokines and by increasing the phosphorylation of intramuscular amino acid-signaling molecules. (5,6)

Nutritional support for oncological patients aims to reduce the loss of body mass and protein degradation. Although catabolism of protein and dry weight loss in these patients can not be completely stopped, nitrogen deficit can be reduced in order to preserve the structural proteins of vital organs.
Calorie intake should meet the caloric needs in order not to consume the energy reserves of the body. Carbohydrates are the main source of energy, and make 60-70% of non-protein calories. Daily requirements for fat in hypermetabolic patient are 25-30% of total calories, which is enough to provide essential fatty acids and energy. Nutrition should maintain balance of nitrogen, or at least minimize its deficit and provide enough amino acids for protein synthesis. In most cases, the requirements for amino acids or protein amounts from 1.0 up to 1.2-2.0 g/kg per day. In cancer patients frequent nutritional assessment is necessary in order to detect early nutritional deficit and introduce nutritional support in time. (5)

2.2. Impact of immobilization due to malignancy on skeletal muscles changes

Bed rest during treatment of malignant diseases leads to loss of condition and decreasing of skeletal mass. For example, a healthy person loses 70g of proteins during two weeks of bed rest. This reduction of proteins due to physical inactivity is a consequence of the loss of stimulating effect of exercise on postprandial anabolic effect of amino acids on muscle protein synthesis, and in this case an increased protein intake is required. Medical rehabilitation includes all methods of physical medicine and rehabilitation, conducted for the restoration of function, especially the locomotor system, but also restoration of other organ systems that have been damaged by malignant disease. Batched, aerobic physical activity and cardiorespiratory rehabilitation prevent further weakening of muscle function, improve efficiency of energy metabolism at the cellular level by increasing functional capacity and thus reducing the subjective feeling of fatigue in these patients. (6)

2.3. Paraneoplastic syndrome

Paraneoplastic syndrome is defined as a clinical syndrome caused by systemic effects of malignancy, but not by the direct influence of metastasis. It is divided into four basic categories: endocrine, neuromuscular, hematologic and mucocutaneous paraneoplastic syndrome.

The most common forms of neuromuscular paraneoplastic syndromes are Lambert-Eaton myasthenic syndrome and dermatomyositis/polymyositis. Lambert-Eaton is basically a presynaptic degeneration of motor nerve endings. It is believed that the target of autoimmune response are voltage-dependent calcium channels. Clinically, the syndrome is manifested by weakness of proximal limbs. The legs are affected more than the arms, there
Skeletal muscles and malignancy

is pain in the muscles, areflexion, and impotence and dry mouth can occur. The basic test for the diagnosis is EMG. It is treated with plasmapheresis and immunosuppressive therapy.

Linkage of dermatomyositis (DM) with malignancy was first described in 1916 but was confirmed much later in randomized clinical trials. Polymyositis may also be associated with malignancy, but the risk is much lower than in the case of dermatomyositis (7). The greatest risk of malignancy in the first year of the occurrence of dermatomyositis, although the risk remains high during 5 years (7).

There are several potential explanations for the association between DM and malignancies including genetic predisposition, infective factors and exposure to toxic chemicals. In addition to genetic predisposition speaks connection of HLADQA1*0301 and anti-p155/140 antibodies in patients with DM (8). These authors have proposed a model of “cross-over” immunity in which an initial cellular immune response is directed at tumor cells overexpressing commonly targeted in myositis. In the setting of muscle injury and regeneration, myositis-specific autoantigens are expressed. An immune reaction initially directed at these autoantigens expressed in tumor cells crosses over and leads to the development of myositis (8).

DM usually occurs in patients with adenocarcinoma of the lung, ovary, cervix, stomach, pancreatic and colorectal cancers. DM may be the first manifestation of malignancy, and sometimes occurs in the later stages of the disease. It is manifested by symmetric proximal muscle weakness. Given that patients with cancer may have a particular weakness of the muscles, muscle biopsy is sometimes necessary for precise diagnosis. DM should be considered in patients with pronounced muscular weakness, loss of weight, elevated serum creatine kinase and liver transaminases. The outcome of DM varies from complete recovery to progressive muscle weakness and deterioration, depending on the course of malignant disease. Patients with paraneoplastic dermatomyositis have skin manifestations often resistant to treatment, severe muscle weakness, respiratory muscle weakness and dysphagia, followed by the presence of anti-P155 antibodies and the absence of conventional antibodies.

3. Influence of malignancy treatment on skeletal muscles changes

Medications are one of the most common causes of diseases of skeletal muscle. The severity of drug-induced myopathies range from mild myalgias with or without weakness, up to severe myopathy with very pronounced muscle weakness and massive rhabdomyolysis with acute renal failure.
The most common toxic effect of vincristine is peripheral neuropathy, however, very often jointed with proximal muscle weakness and myalgia. The toxicity of vincristine is generated from the mechanism of its action – termination of polymerization of microtubules, which results in the change of lysosomal function. Primary histological changes include denervation muscle atrophy, but occasionally areas of segmental necrosis can be seen. Imatinib mesylate, an inhibitor of tyrosine kinase, which is used to treat chronic myeloid leukemia, causes myalgias in up to 50% of patients. Myositis in these patients withdrew after discontinuation of the drug and after administration of corticosteroids. It is believed that myositis associated with imatinib is caused by an autoimmune reaction, since antibodies directed to CML28 (component of the multiprotein complex known as eksozom, which is involved in RNA processing) are found in the blood of these patients (9).

Inflammatory myopathies are also registered in patients with prostate cancer treated with leuprolide acetate. In addition, the recorded cases of rhabdomyolysis are rare in patients who received 5-azacytidine, citabrin, or a combination of cyclophosphamide and mitoxantrone.

Doxorubicin impairs the relaxation of the muscle which is probably associated with changes in microtubules and calcium release resulting from oxidative stress (10).

References
