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Review

Opportunities for rehabilitation of patients with radiation fibrosis syndrome

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ABSTRACT

This review discusses the pathophysiology, evaluation, and treatment of neuromuscular, musculoskeletal, and functional disorders that can result as late effects of radiation treatment.

Although radiation therapy is often an effective method of killing cancer cells, it can also damage nearby blood vessels that nourish the skin, ligaments, tendons, muscles, nerves, bones and lungs. This can result in a progressive condition called radiation fibrosis syndrome (RFS). It is generally a late complication of radiotherapy which may manifest clinically years after treatment. Radiation-induced damage can include "myelo-radiculo-plexo-neuromyopathy," causing muscle weakness and dysfunction and contributing to neuromuscular injury.

RFS is a serious and lifelong disorder which, nevertheless, may often be decremented when identified and rehabilitated early enough. This medical treatment should be a complex procedure consisting of education, physical therapy, occupational therapy, orthotics as well as medications.

1. Background

The status of cancer patient results not only from the direct and indirect effects of the disease but also from treatments such as surgery, radiotherapy, and chemotherapy.[1,2] These treatments may result in musculoskeletal and neuromuscular complications as well as dysfunction of any visceral organ, including the heart, lungs, gastrointestinal tract, and genitourinary tract.[1,3] Radiation-induced toxicity may be a result of acute radiation or a long-term disability following cancer treatment during radiation fibrosis syndrome (RFS).[4,5] RFS can affect any tissue type, including the skin, ligament, tendon, muscles, viscera, nerve, as well as lungs, the gastrointestinal and genitourinary tracts, bone, or other organs, depending upon the treatment site.[6–8] It is generally a late complication of radiotherapy which may not manifest clinically for years after treatment.[9] RFS may cause both functional

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and cosmetic impairment, which can lead to death or a significant deterioration in the quality of life (QoL).

2. Aim

The objective of the study was to review articles about physiopathology, and clinical evaluation of opportunities for rehabilitation in RFS patients.

3. The physiopathology of RFS

RFS is similar to inflammation, wound healing, and fibrosis of any origin. Typical histologic features include the presence of inflammatory infiltrates, particularly macrophages in the earlier stages of fibrosis, differentiation of fibroblasts into postmitotic fibrocytes, and changes in the vascular connective tissue with excessive production and deposition of extracellular matrix proteins and collagen. Among the secreted factors driving fibrosis, is the transforming growth factor beta 1 (TGF-β1) produced by a wide range of inflammatory, mesenchymal and epithelial cells which converts fibroblasts and other cell types into matrix-producing myofibroblasts. After myofibroblast activation, collagen production can be perpetuated independently of TGF-β1 by autocrine induction of a cytokine called connective tissue growth factor.[10] Although TGF-β1 is certainly a key cytokine, the fibrotic process cannot be explained by a single factor. TGF-β1 regulates epidermal growth factor (EGF), fibroblast growth factor (FGF), tumor necrosis factor (TNF α), and IL-1 by stimulating or inhibiting their production in various cell types, including fibroblasts, endothelial cells, and smooth muscle cells.[11] It involves a complex network of interacting cytokines and growth factors, which include radiation fibrosis IL-1, insulin-like growth factor-1 (IGF-1), and TNF α. Three histopathological phases of radiation fibrosis have been described,[10] including: (1) a prefibrotic phase characterized by chronic inflammation in which endothelial cells are thought to play an important role; (2) an organized fibrosis phase with patchy areas of active fibrosis containing a high density of myofibroblasts in an unorganized matrix adjacent to poorly cellularized fibrotic areas of senescent fibrocytes in a dense sclerotic matrix; and (3) a late fibroatrophic phase, characterized by retractile fibrosis and gradual loss of parenchymal cells. The mechanisms linking radiation to chronic vascular dysfunction and subsequent tissue sclerosis, fibrosis, and atrophy are complex and not completely understood. In one theory, Hauer-Jensen et al.[12] postulates that the predominant mechanism by which radiation causes tissue injury in tumors and normal tissues is the induction of apoptosis via free radical-mediated DNA damage. In normal tissues, radiation toxicity occurs in response to a sequence of overlapping events that are attributable to direct radiation-induced changes in cell function as well as indirect responses to tissue injury, causing activation of the coagulation system, inflammation, epithelial regeneration, and tissue remodeling, which is precipitated by molecular signals including cytokines, chemokines, and growth factors. Injury to the vascular endothelium probably plays a role in the response of most normal tissues to ionizing radiation. The abnormal accumulation of fibrin in the intravascular, perivascular, and extravascular compartments may be responsible for the progressive tissue fibrosis and sclerosis that characterizes RFS.[13]

The possible factors that may determine a patient's risk of developing clinical manifestations of RFS include age, medical and degenerative disorders, cancer status, particularly degenerative spine disease, exposure to neurotoxic, cardiotoxic, and other chemotherapy types.[5,14] Another factor in the development of radiogenic lung fibrosis is concomitant tamoxifen therapy as well as location, size of field, and type of radiation.[5,15]

4. Radiation and RFS

Factors associated with a greater risk of RFS include combining other treatment modalities with radiotherapy (i.e. surgery and/or chemotherapy, endocrine therapy), large-volume radiotherapy plans, high total radiotherapy dose, unusually high dose per fraction regimens, coincident infection or operative complications (e.g. wound drainage, and extensive hematoma), and inhomogeneity of dose delivery. The effects of radiation are cumulative, and patients radiated more than once at the same location for recurrent disease can be expected to develop worse radiation fibrosis. Patients given higher than normal doses of radiation are more likely to develop complications. Although subcutaneous radiation fibrosis is probably the most common manifestation of radiation injury, the exact depth in the skin most responsible for the fibrotic process is unclear. Bentzen et al.[16] proposed a range of 3.3–5.5 mm as acceptable reference point for subcutaneous fibrosis in the breast, with the best estimate at the depth of 4.1 mm. They also suggested that the best estimate for the alpha/beta ratio is 1.8 for the fibrosis endpoint. The reason why this may be important is that contemporary 3-dimensional radiotherapy planning systems do not model this dose satisfactorily because it exists in the steep dose gradient build up zone. For subcutaneous fibrosis in the neck tissues, Hirota et al.[16] specified the skin-absorbed dose at the depth of 4.1 mm (*d*4.1-mm depth) in the field center according to the recommendations of Bentzen et al.[16] They found that the *d*4.1-mm depth was affected by the number of fields used and the application of certain techniques such as electron boosts compared with photons. They showed a time dependence in the onset of radiation fibrosis and that patients undergoing prior surgery (neck dissection) have a higher incidence of subcutaneous fibrosis than those without surgery, confirming that the effects of multimodality treatment in addition to the accuracy of dose calculation must be taken into account in estimating late tissue effects. The influence of other factors including total dose as the biologically equivalent dose (BED) at *d*4.1-mm depth, fractionation, and systemic agents are also evident.[17] Dose sculpting techniques include intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy[18] which allows a non uniform coverage of the radiation field to minimize exposure to normal tissues while maximizing the dose to the tumor by shaping the beam to closely approximate its shape in 3 dimensions. The radiation can be controlled to such a degree

that radiosensitive structures such as the spinal cord can be spared, even if they are only a few millimeters away from the tumor.[12] This technique provides for very high doses of radiation to be administered to the tumor volume in fewer fractions, often a single fraction, and has dramatically changed our treatment strategies for many tumors. Some fields of radiation are quite extensive, as in the mantle field radiation port used to treat Hodgkin lymphoma which involves all lymph nodes in the mediastinum, neck (cervical supraclavicular, infraclavicular), or axilla. Patients radiated for head and neck cancer (HNC) are likely to develop RFS due to high dose of radiation. On the other hand, the radiation field can be focal, as when treating isolated vertebral metastasis, extremity sarcoma.[19,20]

5. The complication of RFS

The neuromuscular and musculoskeletal complications of RFS stem from both direct and indirect effects of progressive fibrosis on the nerves, muscle, tendons, ligaments, skin, bones, and lymphatic system. Any level of the nervous system can be affected in RFS. The clinical effects of RFS-induced nerve dysfunction are pain, sensory loss, and weakness. The sequel damage of autonomic nerves may include orthostatic hypotension, bowel and bladder dysfunction, or sexuality dysfunction.[21] Neuropathic pain is an extremely common component of RFS. The mechanisms contributing to the generation of neuropathic pain are complex and involve processes in the central and peripheral nervous system.[22] A factor probably common to the pathogenesis of neuropathic pain in RFS is the generation of ectopic activity in a radiation damaged component of the sensory nervous system. Radiation-induced ectopic activity can develop in any affected neural structure, including the thalamus, ascending spinothalamic tracts of the spinal cord, nerve roots, plexus, and peripheral nerves. The etiology of the ectopic signal can be compressive and/or ischemic with subsequent demyelisation and or axonal loss. Radiation damage to the funiculi of the cervical spinal cord, for instance, can cause pain perceived in any body part caudal to the lesion. This may result in pain in the thorax, abdomen, or lower extremities and mimic radiculopathy, plexopathy, polyneuropathy, or mononeuropathy, with more than one body area, unilaterally or bilaterally, being affected. Peripheral nervous system dysfunction can result from ischemia due to stenosis of the vaso vasorum, from external fibrosis of soft tissues.[23,24] Neuropathic pain is often accompanied by loss or perturbation of sensation. Sensory loss can exist without pain. The primary faculties affected include light touch, pain, temperature, vibration, and position sensation. A deficit in any of these can potentially render the survivor susceptible to other injuries. Similarly, sensory loss can affect gait and performance of activities of daily living. Damage to the nerve roots cause weakness in a myotomal pattern, and fibrosis in muscle fibers within the radiation field can cause focal myopathy. The damage to the cervical paraspinal muscles combined with the damage to neural structures causes the progressive neck weakness and head drop often observed in HNC survivors. Radiation-induced plexopathy can affect the cervical, brachial, and lumbosacral plexus depending on the radiation field and results in functional disability. Mononeuropathies caused by radiation should be obvious when a major structure such as the sciatic nerve is involved in the radiation field.[25] Dysfunction of the dorsal scapular nerve to the rhomboids or the suprascapular nerve to the supraspinatus and infraspinatus is important to the pathogenesis of shoulder dysfunction in many cancer survivors.

5.1. *Muscles*

Myopathic muscles are prone to painful spasms mediated by several pathologic mechanisms, including the myopathy itself, relative weakness and fatigability of muscles. This process may contribute to disorders such as radiation-induced cervical dystonia in HNC patients, in whom the sternocleidomastoid and scalene muscles are affected by radiation resulting in severe spasms and, ultimately, contracture of the neck.[26] The continuous muscle contraction also results in constriction of local blood supply with subsequent tissue hypoxia. Local hypoxia and acidification result in the release of inflammatory mediators, cytokines, and neuropeptides with sensitization of nociceptive nerve fibers. The sensitization of these local pain neurons results in the generalization of muscle pain.[27]

5.2. *Tendons and ligaments*

The effect of radiation on tendons and ligaments is one of progressive fibrosis with consequent loss of elasticity, shortening, and contracture. They can often cause the loss of range of motion in joints and their function. The effects of radiation do not always have to be direct. For instance, radiation to an upper leg can result in marked ankle contracture via effects on the muscles, tendons, and neurovascular innervation of the distal leg.

5.3. *Bone*

Radiation renders bone brittle and proness to injury, including osteoradionecrosis of the mandible, pelvic insufficiency fracture, hip fracture, long bone fracture, rib fracture.[28] Osteopenia and osteoporosis are diseases that are common and potential late-term complications of radiation, leaving patients more susceptible to osteoporotic fractures in later life.[29]

5.4. *Skin*

Radiation-induced dermatitis is a major acute complication of radiation therapy and usually improves in time.[30] Chronic skin changes include progressive fibrosis, sclerosis, and in duration with tenacious and intractable adherence to underlying tissues.

5.5. *Lung*

The early histopathologic findings are described as diffuse alveolar damage. This includes edema of the alveolar walls, intra-alveolar hemorrhage, vessel thrombosis and infiltration with inflammatory cells.[31]

6. Clinical evaluation in RFS

The diagnosis of RFS is not always straight forward. Symptoms can be referable with a history of radiation therapy. It should include all preexisting medical conditions, particularly musculoskeletal, and neuromuscular conditions such as tendonitis, cervical radiculopathy, and neuropathy. The symptoms of RFS can develop during radiation or years later. The details of the patient's pain, spasm, tightness and the language they use to describe their symptoms are important. Signs may be nonspecific, but often described as "pulling", "cramping". Neuropathy terms such as "stabbing", "searing", and "burning" can be used to describe the pain associated with nerve injury. Physical examination is of paramount importance in understanding, and treating the clinical manifestation of RFS. Imaging is often useful in the evaluation of RFS. Magnetic resonance imaging (MRI) is the test of choice for evaluating the spine, soft tissue, joints. Computer tomogram (CT) in contrast is usually used to image the viscera of the chest, abdomen, and pelvis. Electrodiagnostic (electroneurography – ENG, electromyography – EMG) is useful to identify, localize, confirm, and differentiate radiculopathy, plexopathy, neuropathy, or myopathy in patients with RFS.[1]

7. Rehabilitation

Rehabilitation has enjoyed tremendous success in relieving pain and improving the function and QoL of cancer survivors.[3,32] Rehabilitation using extensive training in neuromuscular and musculoskeletal medicine as well as in the principles of functional restoration is uniquely positioned to help direct efforts to improve QoL for cancer survivors with RFS. The main goal of the maintenance of the rehabilitation in chronic conditions is improvement of the affected body function and an increase in daily activities. This treatment has to be a complex procedure consisting of education, physical therapy, occupational therapy, orthotics as well as medications.[1]

7.1. *Education*

Education is of paramount importance to cancer survivors with RFS. Patients are, in general, extremely grateful when they have a practitioner who will listen to them and try to understand their complaints. They become hopeful when the basic physiopathology and interrelationship of their disorders are understood and explained to them.[33]

7.2. *Physical therapy*

The principles of physical therapy (PT) in cancer, the use of therapeutic modalities and therapeutic exercise have been discussed extensively.[3,34–36] Physical activity during radiotherapy has a positive effect on most parameters such as QoL, fatigue, and fitness.[34–39] In patients with RFS, exercise should be done to extend the range of motion in joints, and increase muscle strength. In the case of loss (atrophy) of muscle, synergistic muscles exercises can be introduced to compensate this. PT, which should be postural retraining through core strengthening, flexibility and conditioning of the muscles. Although these muscles are impaired, they often respond well to rehabilitative efforts, and even small gains in muscle stamina coupled with improved posture can translate into large functional improvement for the patient. Correction of anatomic posture alone will help decrease energy expenditure and pain in most patients. Because the fibrotic process that underlies RFS cannot be directly affected, insidious progression of weakness and dysfunction is ultimately unavoidable. The adherence to a life-long exercise program emphasizing home maintenance exercises is of paramount importance to help maximize and maintain function and QoL. After the systemic therapy, patients require exercises of general fitness type in order to improve their physical efficiency.[35,36] In patients undergoing tumor treatment, the use of selected manipulative techniques was reported that concerned patients with breast cancer, HNC tumors and gastric carcinoma.[40–42] RFS may cause deformation and function disorders of the fascial system that exerts a crucial influence on the mobility of joints, abdominal and lumbar tissues, and consequently, of chest walls.[40,42] The fascial techniques consisting in expanding the skin, subcutaneous connective tissue and deep fascia make it possible to restore normal shifting of particular layers of soft tissues.[39,42] The myofascial relaxation was found to influence the general homeostasis thanks to the loosening of tense soft tissues enabling to reduce pain and improve circulation in the region with RFS. In the process of patient recovery, visceral manipulations were used to eliminate the dysfunction in the region of internal organs and muscles through restoring normal mobility, flexibility and tension of tissues surrounding a given organ and thereby causing better blood supply in the organ.[40,41]

7.3. *Orthotic*

The role of orthotic in the management of RFS follows the same basic principles of orthotic use as in other neuromuscular and musculoskeletal disorders. The various designs of cervical orthotics should be applied to control neck extensor weakness. The biomechanical principles of their balance are basic to the kinesthetic skeletal fixation.[43] When rehabilitative efforts are inadequate to maintain adequate posture and pain relief, a cervical orthotic (cervical collar) should be considered. This is not intended for continuous use; it should be used as an energy conservation device, instead. Patients with difficulty in maintaining their head in an upright position or who experience pain as the day progresses because of muscular overload should wear the collar whenever possible. Activities to use the collar include housework, eating, working with the computer, watching television, and reading. Upper extremity orthotic is used to improve function in patients with sever radiculopathy or plexopathy.[44] Lower extremity orthotics may be used for patients with dorsiflexion weakness, including myelopathy, plexopathy (lumbosacral trunk), radiculopathy. The ankle foot orthotics (AFO's) is preferable for use when the plantar flexion weakness and inability to control the ankle is present. They are small, light and provide good functional benefit.[45] A solid AFO is only appropriate when severe spasticity must be controlled, and this is the case in RFS survivors as deficits

most commonly affect the peripheral nervous system.[45] If knee extension weakness and difficulty with dorsiflexion are present, the knee immobilizer may be used.[46]

7.4. *Medications*

Medications are needed to control pain and muscle spasms in RFS. In patients with neuropathic pain, treatment with nerve stabilizer is indicated in the first line. Opioids are often added to either or both pregabalin and duloxetine when needed. Newer agents, particularly pregabalin, are generally preferred rather than older agents such as the tricyclic antidepressants because they have efficacy and little potential for drug–drug interactions.[47] Nonsteroidal anti-inflammatory drugs are generally recommended when pain from inflammation of adhesive capsulitis, degenerative changes is diagnosed. Opioids relieve pain but are not effective for muscle spasm and other neuropathic symptoms. They should generally be reserved for second-line use or added to nerve-stabilizing agents when treating pain in RFS. Muscle relaxants including baclofen, and bezodiazepines may help relieve the pain associated with muscle spasms.[48] Trigger-points injection is simply an injection of local anesthetic into the area of a painful muscle spasm. It may be of benefit to patients with muscle pain in the trapezius, rhomboids, cervical paraspinal muscles.[49,50] Botulinum toxin injection has a potential benefit in several specific complications of RFS, including cervical dystonia, trismus, painful muscle spasms, spasticity, and focal neuropathic pain disorders.[26,51,52]

7.5. *Prevention of RFS*

The prevention of radiation-induced fibrosis has focused on the improvements in RT technique, which have resulted in higher doses to the tumor target and decreased doses to normal tissue, thus potentially preventing the development of radiation-induced fibrosis. Furthermore, established radiation-induced fibrosis may be treatable with novel therapeutic approaches, particularly the combination of pentoxifylline and vitamin E.[53] With the progress of clinical research, Chuai et al.[31] believe that hydrogen-rich solution will give us more hope for the prevention of radiation pneumonitis.

8. Conclusion

RFS is a serious and lifelong disorder. Various complications of RFS are usually treatable although they require vigilance on the part of the physician. When the treatment is conducted along with rehabilitation, and when identified early, these disorders are often decremented.

Conflict of interest

None declared.

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