Pathophysiology and Treatment of Radiation-Induced Brachial Plexopathy

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ABSTRACT

Radiation therapy is a well proven effective treatment modality in the management of various cancers. However, radiation therapy has potentially adverse effects on several tissues including central and peripheral nervous systems. Radiation-induced brachial plexopathy is a rare but challenging complication of RT in patients undergoing chest, axillary, and neck irradiation because of myriad of primary or malignant tumors of these region. It is a progressive disease state which may lead to devastating sensorial and motor malfunctions. Currently, there is no generally accepted treatment method, but non-narcotic and narcotics and anesthetic interventions for grade 1 and 2 lesions are suggested. In grade 3 and 4 injuries, surgical interventions to prevent fibrosis of the vascular supply to the nerves and to release nerves from fibrotic constrictions should be considered.

Key Words: Brachial plexus, Plexopathy, Radiation therapy

ÖZET

Radyasyona Bağlı Brakial Pleksus Hasarının Patofizyolojisi ve Tedavi Seçenekleri

Radyoterapi birçok kanser türünün tedavisinde başarıyla kullanılmakta olan tedavi seçeneklerinden biridir. Ancak, radyoterapi merkezi ve periferik sinir sistemini de içine alan bir çok dokuda hasar oluşturma potansiyeline sahiptir. Bunlardan biri de nadiren görülmesine rağmen önlenmesi oldukça güç olan brakiyal pleksus hasarıdır. Radyasyona bağlı brakiyal pleksus hasarı göğüs, aksilla ve boyunu kapsayan alana primer veya metastatik tümörlerin tedavisi amacıyla radyoterapi uygulanan hastalarda görülmektedir. Pleksus hasarı genellikle progresif bir seyir izleyerek duyusal ve motor bozukluklara yol açabilir. Günümüzde literatürde genel kabul görmüş bir tedavi seçeneği bulunmamaktadır. Ancak, genel olarak uygulanacak tedavi modaliteleri daha çok hasarın derecesine göre seçilmektedir. Grad 1 ve 2 pleksus hasarlarında narkotik ve narkotik olmayan ağrı kesicilerin kullanılması ve anestetik girişimler yeterli olmaktayken, grad 3 ve 4 hasarlarda sinirin fibrotik dokulardan serbestleştirilmesi ve sinirin kanlanmasını sağlayan vasküler yapılarda fibrozis gelişmesini önlemeye yönelik cerrahi girişimlerin uygulanması gerekmektedir.

Anahtar Sözcükler: Brakiyal pleksus, Pleksus hasarı, Radyoterapi

INTRODUCTION

Radiation therapy (RT) is effectively used in the treatment of a myriad of primary or metastatic malignant diseases of chest, axillary and head and neck regions. However, RT has potentially adverse effects on several tissues including central and peripheral nervous systems. Radiation-induced brachial plexopathy (RIBP) is one of the rare but dose limiting and severely debilitating complications of RT which can occur when RT is directed at the chest, axillary region, thoracic outlet, or neck.

The incidence of RIBP is estimated to be in the range of 1.8% to 4.9%, and is most commonly reported in patients undergoing RT because of breast or lung primaries (1-3). There is no evidence in the literature considering a relationship between RIBP occurrence and any racial or ethnic groups. Although, no age group has been suggested to be more prone to develop RIBP, the age distribution closely parallels that of patients with breast cancer. Similarly, given that breast cancer often is treated with RT, women experience a greater incidence and prevalence of RIBP than men.

With the present review, the literature evidence considering the pathophysiological and clinical features and treatment of RIBP which is a scarcely reported but severely debilitating complication of RT, has been aimed to be summarized.

Anatomy and Neurophysiology of Brachial Plexus

The brachial plexus is a network of nerves formed by intercommunications among the ventral rami of the lower four cervical nerves (C5-C8) and first thoracic nerve (T1). The brachial plexus is located near where the neck joins the shoulder, behind the clavicle and between the spine and the upper arm, just distal to the axilla. The nerves from the spine join and split in a pattern that forms five sections of the brachial plexus: roots, trunks, divisions, cords, and nerves. The brachial plexus with its five major terminal nerve endings (axillary, radial, ulnar, median, and musculocutaneous) is responsible for motor innervation of almost all muscles of the upper limb excluding trapezius and levator scapula muscles. Similarly, all cutaneous innervation of the upper limb with the exception of the area of axilla, an area just above the point of the shoulder, and the dorsal scapular area, is supplied by the brachial plexus. The simplified anatomical structure of the brachial plexus has been shown in Figure 1.

Pathophysiology

The peripheric nerves were believed to be relatively radioresistant because of their low metabolic rate and almost absent reproductive capacity, which may be related with very short follow-up times in the past studies (4,5). However, the effects of irradiation on peripheric nerves begin as early as in first 48 hours following RT, and include: enzyme changes, bioelectrical alterations, altered vascular permeability, and abnormal microtuble assembly (4,6). Mendes et al (6) described two phases of radiation induced neuropathy in which the first phase includes bioelectrical and histochemical alterations, whereas the second phase relates with late fibrosis of the tissue surrounding the nerves. RIBP may be initiated by the damage to the nerve or due to entrapment of the nerve fibres by fibrosis of the connective tissues of the axillary or neck regions (7,8). Necrosis and hyalinization of the media of small arteries, replacement of nerve fibers by fibrotic tissues, demyelination and thickening of epi- and perinerium are the morphological changes observed in RIBP (4,9,10). Fibroblasts, large amounts of various extracellular matrix components, and infiltration with inflammatory cells are found in the degenerated fibrotic connective tissue (8). The development of fibrosis is a slow process which in general has a latency period of 1 to 4 years (11-14), but may be as long as 6 to 22 years (7,8,15,16). Furthermore, the incidence of brachial plexopathy increases with time after RT (4,13). In the study reported by Bajrovic et al (7) including 140 breast carcinoma patients of whom 19 had had RIBP, freedom from plexopathy was 96.1%, 75.5%, 72.1%, and 46% at 5, 10, 15, and 19 years of follow-up respectively. Although, very short periods of latency have also been reported, they should be related with abnormal genetic susceptibility (7,17-19). However, some patients carry higher risk for evolution of RIBP, including those whom were treated with fraction doses >2 Gy, total doses higher than 60 Gy, overlapping fields, increased dose in axilla because of a smaller separation at that point, use of less

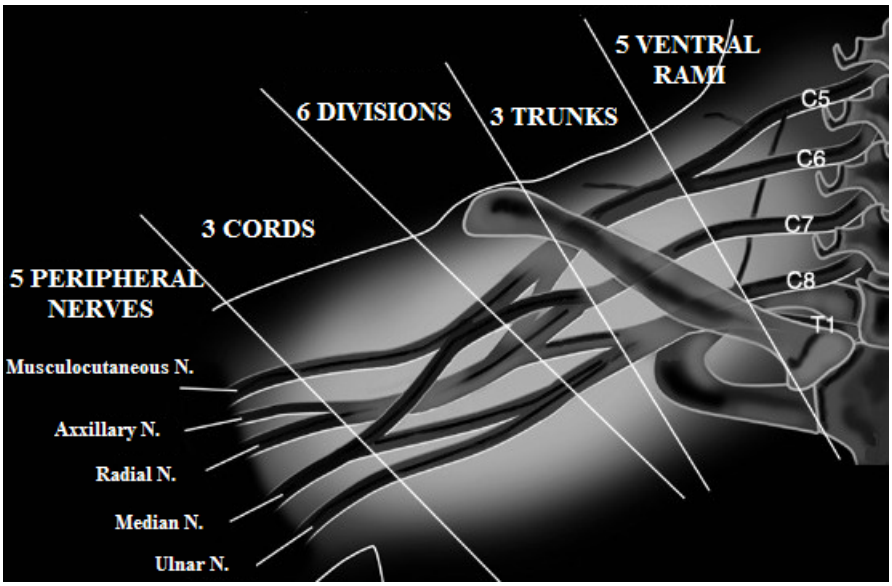

Figure 1. Simplified anatomical structure of brachial plexus

than three irradiation fields and concurrent administration of chemotherapy (1,12,15,20). Powell et al (12) used two different fractionation schemes: first group of patients were treated with 3 Gy/fr (total; 45 Gy), and the second group was treated with 1.8 Gy/fr (total; 54 Gy). The incidence of RIBP was reported to be 5.9% and 1%, for 3 Gy/fr and 1.8 Gy/fr doses, respectively. The risk factors which increase both probability of occurrence and severity of RIBP are further discussed in "Treatment and Prevention" section.

Clinical Features and Differential Diagnosis

Although, the interval from the last dose of radiation to the first symptom of plexopathy varies widely, the median interval range reported is 4.5 months to 6 years (17,11,12,21). The sensory symptoms, such as numbness, paresthesia, and dysesthesia, along with swelling and weakness of the arm, are the predominant presenting symptoms. One series reported that 55% of patients presented with paresthesia, and the remainder had arm swelling and weakness (8-11). These neurological symptoms can be progressive resulting with a weak and edematous arm. Only 18% of patients presented with any significant pain, and pain was a major symptom in only 35% of patients. The pain symptoms usually are limited to the shoulder and proximal arm, and such pain usually is rated as mild to moderate in intensity (11,12,21,22). Bajrovic et al (23) graded plexopathies in 4 by using LENT-SOMA scale: grade 1) mild sensory deficits, no pain; grade 2) moderate sensory deficits, tolerable pain, mild arm weakness; grade 3) continuous paraesthesia with incomplete motor paresis, pain medication required; grade 4) complete motor paresis, excruciating pain, muscle atrophy. The incidence of isolated motor dysfunction is extremely rare (23). The RIBP is a progressive clinical entity in which upgrading from grade 1 to 2 lesions to grade 3 or 4 during observation period is possible (7).

On neurologic examination, findings are most prominent in the C5-C6 myotomes and dermatomes, as well as diminished deep tendon reflexes supplied by C5-C6. However, Schierle and Winograd (24) reported frequent involvement in the C7 distribution. Myokymia is difficult to visualize by inspection or palpation. In the series by Monidrup (25), 78% of patients with RIBP presented with upper trunk involvement. The lymphatic-vascular system may reveal prominent lymphedema of the involved extremity without cyanotic or dusky features. There should be no disturbance of arterial or venous circulation in the involved extremity and no changes in the limb to suggest venous insufficiency. Horner syndrome is not present in patients with RIBP. The musculoskeletal examination may reveal decreased

Table 1. Differential Diagnosis

Neoplastic Brachial Plexopathy
Cervical Disc Disease
Brachial Neuritis
Cervical Myofacial Pain
Traumatic Brachial Plexopathy
Radiation Fibrosis
Transient Radiation Injury
Acute Ischemic Injury
Mononeuritis Multiplex
Cervical Spondylosis
Neuralgic amyotrophy
Subacromial bursitis
Supraspinatus tendonitis
Paraneoplastic syndrome

scapulothoracic and glenohumeral joint range of motion. This development is not secondary to the plexopathy; rather, it may be experienced if (a) previous surgery was performed in the chest wall or axillary region or (b) the finding is secondary to fibrosis of the musculoskeletal tissues from the RT. No specific joint tenderness or effusions should be encountered during the examination of the involved extremity.

Many disorders including neoplastic brachial plexopathy, infectious, inflammatory, and traumatic plexus injuries may mimic RIBP (Table 1). The differential diagnosis between radiation-induced and neoplastic brachial plexus injury is a difficult problem that remains to be solved (4,7-9,11,18,26,27). The diagnosis of RIBP is based on clinical history and examination, electromyography (EMG), ultrasonography (USG), computerized tomography (CT), and magnetic resonance imaging (MRI). The EMG findings of RIBP include reduction in amplitude, slowing of conduction velocity and increase in latency (1,7). Myokymia is a finding of RIBP which is absent in tumor recurrence (28). Currently EMG does not play an important role in discrimination of tumor injury from RIBP. Similarly, CT was the first useful diagnostic tool to show tumoral involvement of brachial plexus, but now MRI is the preferred imaging modality used to discriminate RIBP from neoplastic brachial plexopathy (7,8,18). Radiation fibrosis may appear as high and low intensity fields on T2-weighted images on MRI (7), and furthermore in report of Hoeller et al8 MRI was successful in exclusion of tumor recurrence but no reliable specific sign that can be attributed to RIBP was identified on MRI. Positron emission tomography (PET) imaging as a new tool may provide an additional tool for excluding suspected malignant plexopathy. In contrast with radiation induced fibrosis and RIBP, malignant etiologies of brachial plexopathy are associated with significantly increased uptake of 18-fluoro-2-deoxy-D-glucose, reflecting the increased metabolism associated with neoplastic processes (3). Ultrasonographic examination may be beneficial in some cases but the definite diagnosis relies on histopathological examination (13).

Treatment and Prevention

Treatment of RIBP consists of transdermal electrical nerve stimulation, dorsal column stimulation, neurolysis, neurolysis with omentoplasty, physical therapy, hyperbaric oxygen therapy tricyclic antidepressants, anticonvulsives, non-steroidal anti-inflammatory drugs, non-narcotic and narcotic analgesics, anesthetics and steroids (29,30). In management of RIBP the first but the most important step must be the discrimination of RIBP from that metastatic plexus involvement. Following definite diagnosis of RIBP, the treatment is planned on the basis of grade of severity of injury. In grades 1 and 2, generally conservative treatment consisting non-narcotic and narcotic analgesics and anesthetic interventions are required (4,7,11). In grade 3 and 4 injuries surgical exploration is needed (4,7,26). Surgical intervention allows the release of neural elements from fibrotic tissue bundles and prevents the fibrosis of the vascular supply of the nerves (4). In one study Narakas (24) proposed omentoplasty as a treatment method but the results were not satisfactory. In another study Pritchard et al (23) randomized 34 volunteers with RIBP to hyperbaric oxygen therapy or a control groups. Normalization of the warm sensory threshold was seen in two of the patients receiving hyperbaric oxygen therapy. Furt-

her two patients with chronic arm lymphedema reported significant improvement in arm volume. But the authors concluded that, although these results were justifying further investigation, still there was no reliable evidence to support hyperbaric oxygen therapy to prevent or reverse RIBP.

Efforts to prevent rather than treat the RIBP may be more valuable, but it is a difficult challenge as the tumor response closely depends on radiation dose and portal size. Reduction of field size and total dose of radiation were proposed to decrease the incidence of RIBP (4). Moody and Williams (31) suggested decreasing total RT dose from 40 Gy to 32.5 Gy in patients with Hodgkin's lymphoma. In another study Pierce et al (1) found that the RIBP was more commonly experienced by patients those who received greater than 50 Gy total dose to axillary region (P: 0.004). However, besides total dose, the treatment technique (two versus three fields; P: 0.0009), and concomitant use of chemotherapy were also significantly affecting the incidence of RIBP. Chemotherapy was reported to increase RIBP incidence (13,15,32). Specifically the vinca alkaloids reduce the anterograde axoplasmic transport and consequently increase the nerve susceptibility to chronic compression (32). In series of Olsen et al (33) patients who received chemotherapy had a higher incidence of brachial plexopathy than those receiving radiation alone. However, in reports of Bajrovic et al (7), and Gillette et al (4) appeared to have no impact on the rate of RIBP. Thus, the exact role of chemotherapy on occurrence and severity of RIBP remains to be investigated.

CONCLUSION

Radiation-induced brachial plexopathy is a rare but difficult to prevent complication of RT in patients undergoing chest, axillary, and neck irradiation because of myriad of primary or malignant tumors of these region. It is a progressive disease state which may lead to devastating sensorial and motor malfunctions. Currently there is no accepted guideline for its treatment, but non-narcotic and narcotics and anesthetic interventions for grade 1 and 2 lesions are suggested. In grade 3 and 4 injuries, surgical interventions to prevent fibrosis of the vascular supply to the nerves, and to release nerves from fibrotic constrictions should be considered.

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