Fast Neutron Therapy for Malignant Myxoid Fibrous Histiocytoma

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Abstract— Malignant fibrous histiocytoma (MFH) has been regarded as the most common soft tissue sarcoma (STS) in adults. Management typically includes complete resection followed by or preceded by radiation therapy but when this is not possible management can be quite challenging. Conservative surgery combined with post-operative radiotherapy is standard treatment of limb and truncal tumours in the UK and achieves high rates of local control whilst maintaining optimal function. Yet its true nature and the validity of this diagnostic concept have increasingly been questioned. Available data suggest that most patients with MFH can be subclassified into specific STS types, but the clinical relevance of such categorization has been argued. We describe a patient with this disease treated with Fast Neutron Therapy and its successful outcome.

Index Terms— Histiocytoma, Neutron therapy, Palliation, Sarcoma

I. INTRODUCTION

Soft tissue sarcomas are a rare and heterogeneous group of malignant tumors, representing under 1% of all adult malignancies. [1] About 60% of soft tissue sarcomas occur in the extremities, making this the most common site. Other common locations are the trunk (19%), the retroperitoneum (15%), and the head and neck (9%). Malignant fibrous histiocytoma (MFH), a type of sarcoma, is a malignant neoplasm composed of fibroblasts, myofibroblasts, and histiocytes but of uncertain origin that arises both in soft tissue and bone. MFH is the most frequent soft tissue tumor in adults; primary osseous MFH develops far less often. Soft tissue MFH occurs in the extremities 70-75% of the time with about 50% of all cases occurring in the lower extremity [1]. Other less common sites include the retroperitoneum and the head and neck. The peak incidence is during the fifth through seventh decades of life and there is a male to female ratio of 1.5 to 1. In about 20% of cases MFH may arise secondary to another process such as surgery, fracture, osteonecrosis, Paget's disease, non-ossifying fibroma, fibrous dysplasia or radiation exposure. [2] MFH arising from a previous abnormality may behave more aggressively and portend a poorer prognosis than primary MFH. Primary osseus MFH is typically a central lesion in the diaphysis or metaphysis of the bone resulting in aggressive bone destruction and an accompanying soft tissue mass. The most common sites in descending order are the distal femur, proximal tibia, proximal femur and proximal humerus.

The name malignant fibrous histiocytoma was first introduced in 1961 by Kauffman and Stout [3] and controversy has plagued it since. They described MFH as a tumor rich in histiocytes with a storiform growth pattern. Multiple subtypes have been defined including storiform-pleomorphic, myxoid, giant cell, and inflammatory variants. By 1977, MFH was considered the single most common soft tissue sarcoma of adult life. In 2002, the World Health Organization (WHO) renamed MFH as an undifferentiated pleomorphic sarcoma, not otherwise specified. [4]

Soft tissue sarcomas are classified histologically according to the soft tissue cell of origin. Additional studies, including electron microscopy, specialized immunohistochemistry, flow cytometry, cytogenetics, and tissue culture studies may allow identification of particular subtypes within the major histologic categories. For example, S100 antigen suggests neural sheath origin, cytokeratin suggests epithelioid or synovial cell origin, and factor VIII-related antigen suggests endothelial origin. Likewise, some subtypes of sarcomas have characteristic genetic markers, but these markers are not generally used in the routine clinical setting (e.g., t(X;18)(p11;q11) in synovial sarcomas and t(12;16)(q13;p11) in myxoid and round-cell sarcomas).[5-7]

The histologic grade reflects the metastatic potential of these tumors more accurately than the classic cellular classification listed below. Grade is based on the number of mitoses per high-power field, the presence of necrosis, cellular and nuclear morphology, and the degree of cellularity. Discordance among expert pathologists regarding tumor grade, and even histologic subtype, can be substantial [8]. Surgery remains the mainstay
of treatment of all soft tissue sarcomas. When feasible, function sparing surgical excision with wide margins is the cornerstone of management, the goal being preservation of a functional extremity [9]. Retroperitoneal location generally confers a more ominous prognosis as compared to other sites. When surgery is not possible, conventional radiotherapy is not usually considered a realistic alternative for adult soft tissue sarcomas. Here we describe the successful treatment of an 83 year-old male patient treated definitively with fast neutron therapy.

II. CASE REPORT

An eighty three year-old white male was diagnosed with malignant myxoid fibrous histiocytoma (MFH) of the right flank in 1996 when he presented with a palpable mass. The mass was surgically removed. Unfortunately it locally recurred at least five times; the last one was in 2006. Each recurrence was treated with surgery. The Computerized Tomography (CT) scan of the chest on 3/12/07 showed recurrent mass measuring 5.7 x 11.7 cms and extended to involve the right quadratus lumborum muscle (Image-1). A repeat surgery would have involved extensive chest wall resection and reconstruction. As an alternative option the patient was recommended High Energy Fast Neutrons and he was seen at Northern Illinois University Institute for Neutron Therapy (NIU INT) at Fermilab in Batavia, Illinois in consultation. On examination, the patient appeared to be younger than his stated age; his Karnofski scale at 100. There was no palpable cervical adenopathy. There was right chest deformity with scoliosis as a result of multiple surgeries and resection of right sided ribs. There was right lateral abdominal wall hernia. On his back close to the midline there were two palpable masses. The one near the scapular wing measured 15 x 11.5 cms. It was ill defined soft and non-tender. The other soft tissue non-tender mass was adjacent to the spine, just 2 cm caudal to the one above, measured approximately 5 x 5.5 cms. (Image-2) After the evaluation it was felt that he was an appropriate candidate for Fast Neutrons. The patient underwent Neutron radiation therapy planning procedure with a vertical CT scanner. He was treated standing in an immobilization device on a treatment platform which functions as an isocentric gantry with capabilities of 360 degree rotational, front to back and side to side movements to accommodate the fixed neutron beam. A neutron beam (produced by 66 MeV protons striking a beryllium target) with a central-axis depth dose profile similar to a 6 MeV photon beam was used for the therapy. Fixed dimension concrete/polyethylene collimator inserts with steel hand blocks were used for field definition. The computer generated isodose treatment plan was complex. The length of the field and variations in the transverse dimensions of the tumor necessitated splitting the field along the body axis. This allowed beam angles and wedges to be manipulated to best conform to the tumor (Image-3). The match between upper and lower fields was staggered. A dose of 20.4 Gy of Neutrons was delivered in 12 fractions at 3 fractions per week over 26 days. The patient tolerated the treatment exceedingly well. He had mild skin reaction that was managed with topical moisturizers. At 2 yrs 3 months follow-up there were no complications.
The most recent CT scan showed marked area was woody and hard and there was localized telangectasia mild skin and subcutaneous tissue changes were seen. The palpable masses in the back. However, post neutron therapy 2 years post treatment. No residual mass, minimal skin erythema. area was woody and hard and there was localized telangectasia (Image- 4). The most recent CT scan showed marked improvement of the posterior chest wall mass (Image-5).

III. DISCUSSION

MFH manifests a broad range of histologic appearances with four sub-types described [10]: 1) Storiform-pleomorphic 2) Myxoid 3) Giant cell 4) Inflammatory. Of these, the storiform-pleomorphic is the most common type, accounting for up to 70% of most cases. The myxoid variant is the second most common accounting for approximately 20% of cases. Unlike the other sub-types of MFH, the myxoid form tends to be less aggressive and as a result is associated with a better prognosis. Giant cell and inflammatory types are rare. Inflammatory MFH tends to occur in the retroperitoneum. As with all sarcomas of soft tissue and bone, MFH is rare, with just a few thousand cases diagnosed each year. MFH of soft tissue typically presents in a patient that is approximately 50 to 70 years of age though it can appear at any age. MFH is very rare in persons less than 20 years old. There is a slight male predominance. Soft tissue MFH can arise in any part of the body but most commonly in the lower extremity, especially the thigh. Other common locations include the upper extremity and retroperitoneum. Patients often complain of a mass or lump that has arisen over a short period of time ranging from weeks to months. It is not uncommon for patients to report trauma to the affected area. Trauma as far as we know does not cause MFH but rather the incident draws attention to the extremity. The mass does not usually cause any pain unless it is compressing a nearby nerve. Symptoms such as weight loss and fatigue are not typical but can present in patients with advanced disease. Retroperitoneal tumors can become quite large before they are detected as patients do not feel a mass palpable masses in the back. However, post neutron therapy mild skin and subcutaneous tissue changes were seen. The area was woody and hard and there was localized telangectasia (Image- 4). The most recent CT scan showed marked improvement of the posterior chest wall mass (Image-5).

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In an older study of 211 patients with high-grade soft tissue sarcomas of the extremities at the NCI (National Cancer Institute), there was no difference radiotherapy in disease-free or overall survival between patients undergoing radical amputation compared to those undergoing limb-sparing procedures plus postoperative radiation therapy [12]. Since then, limb-sparing therapy with adjuvant radiotherapy to complement adequate surgery has become standard treatment for intermediate and high-grade soft tissue sarcomas. Radiotherapy can be preoperative or postoperative radiation, depending on institution protocols [13]. Preoperative radiotherapy can occasionally permit limb conservation of extremity sarcomas that otherwise would be inoperable or require amputation [14]. Some reports suggest that preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy but the size of the radiotherapy port may be considerably smaller in the preoperative setting [13]. That same preoperative vs postoperative study demonstrated that overall survival was slightly better in patients who had preoperative radiotherapy than in those who had postoperative treatment. Brachytherapy (in which the radiation oncologist places hollow tubes into the tumor bed for postoperative loading with Iridium-192 wires) either exclusively or in combination with postoperative external beam radiation, is an option that is also occasionally employed. This delivers radiation directly to the surgical bed while minimizing irradiation of healthy nearby tissues [15]. Intensity-modulated radiation therapy (IMRT) is currently under investigation for retroperitoneal sarcomas as it can target the delivered radiation dose with greater precision and this should be associated with less morbidity. Some reports confirm diminished toxicity with this strategy but local recurrence remains common. Dose escalation with IMRT is under investigation.

The treatment options are limited for locally recurrent and unresectable sarcomas. Sarcomas are categorized into so-called radioresistant cancers, not responsive to conventional photon radiation therapy. However, Particle beam, High-energy Fast Neutron therapy has been used in the treatment of sarcomas, either as an adjuvant modality with surgery or definitively as a single modality for recurrent, unresectable or residual tumor. Neutron therapy is a highly effective form of radiation therapy. Radiation therapy is the use of penetrating beams of ionizing radiation, primarily to treat...
cancerous/malignant tumors. Conventional radiation therapy includes photon (x-ray) and electron radiation, which is available at many clinics and hospitals. These beams are produced by electron accelerators or from radioactive sources such as cobalt. Hadron therapy includes neutrons and protons, which are generated using proton or deuteron accelerators. The basic effect of ionizing radiation is to destroy the ability of cells to divide, by damaging their DNA strands. For photon, electron and proton radiation damage is done primarily by activated radicals produced from atomic interactions. These types of radiation are called low linear-energy-transfer (low LET) radiation. Neutrons are high linear-energy-transfer (high LET) radiation and the damage is done primarily by nuclear interactions. If a tumor cell is damaged by low LET radiation it has a good chance to repair itself and continue to grow. With high LET radiation the chance for a damaged tumor cell to repair itself is very small.

In general, fast neutrons can control very large tumors, because unlike low LET radiation, neutrons do not depend on the presence of oxygen to kill the cancer cells. In addition, the biological effectiveness of neutrons is not affected by the time of stage in the life cycle of cancer cells, as it is with low LET radiation. It often happens that large tumors have metastasized (spread) to other parts of the body before the patient seeks treatment. In these cases neutrons can be used to control the primary tumor, but chemotherapy must be used to limit the spread of cancer through the rest of the body. Because the biological effectiveness of neutrons is so high, the required tumor dose to kill cancer cells is about one-third the dose required with photons, electrons or protons. A full course of neutron therapy is delivered in only 10 to 12 treatments, compared to 30 - 40 treatments needed for low LET radiation [16].

Soft tissue sarcomas were treated in most of the neutron therapy centers, mainly because they are often resistant to X-rays and also because of the excellent results reported from Hammersmith (Catterall and Bewley, 1979). Historically, the local control rate of unresectable soft tissue sarcomas with photons is between 30 to 45% [17-19]. The international and national local control rate for soft tissue sarcoma with neutrons is reported to be between 53% and 76% [20, 21]. Fast neutron beam therapy has also been used for palliation for local symptoms.

Schwartz D.L., et. al. [22] reported the results of treating 89 lesions in 72 patients with fast neutrons, with soft tissue sarcomas; of these, 34 lesions were treated with a palliative intent. Median follow-up for palliative ents was 6 months (range 2-47). Estimated local relapse-free survival at 1 year was 62%. Clinical response rate was 78%. For curative patients probability of local relapse survival, distant disease-free survival, cause specific survival, and overall survival were 68%, 59%, 68%, and 66% respectively. The authors concluded that fast neutron radiotherapy is locally effective for soft tissue and cartilaginous sarcomas with high-risk features. In a palliative setting, neutrons frequently provide significant symptomatic response for gross disease with minimal serious chronic sequelae. They also concluded that fast neutron radiotherapy should be considered in patients at high risk for local recurrence in both curative and palliative settings.

IV. CONCLUSION

This case report can serve as hypothesis generating for a prospective trial testing the safety and efficacy of neutrons in the treatment of locally recurrent, resectable soft tissue sarcomas. It is also an effective treatment modality for palliation of local symptoms for these patients and should be considered.

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