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Systemic Lupus Erythematosus diagnosed with extreme skin reaction during radiation therapy: a case report

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The use of breast conservation therapy in patients with collagen vascular disease is controversial. Initial reports demonstrated severe skin reactions in patients receiving radiotherapy who also had a diagnosis of systemic lupus erythematosus or sclererderma. However, a more recent case-control study found no increased incidence of complications in these patients compared to patients without collagen vascular disease. We report a case of a patient diagnosed with systemic lupus erythematosus after developing a severe skin reaction early during her course of breast radiotherapy. The clinical course of the patient is reviewed along with the controversies surrounding this clinical dilemna.

Key words: breast neoplasms-radiotherapy; lupus erythematosus, systemic

Introduction

Breast conserving surgery is gaining popularity in the treatment of stage I and II breast carcinoma. Lumpectomy, with or without, axillary dissection and radiation therapy results in a similar local control and survival rate when compared to modified radical mastectomy. Many of the contraindications to such therapy are clearly outlined.[1] Collagen Vascular Disease (CVD) remains a controversial issue in the field of radiation therapy at this time. CVD is considered a relative or absolute contraindication to the utilization of radiation in breast conserving therapy. The literature was reviewed following this case presentation to illustrate current beliefs. The questions raised by this case warrants a discussion of what course to take when the diagnosis of Systemic Lupus Erythematosus (SLE) is made during treatment with external beam irradiation.

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Case history

A 38 year old Caucasian woman was evaluated following a routine mammography which showed calcifications of the left breast. This suspicious lesion was evaluated with fine needle guided biopsy. The official pathology revealed a foci of lobular carcinoma in situ measuring 1.5 cm in greatest dimension. She subsequently underwent left breast lumpectomy with axillary node dissection. Patholog-

ic examination revealed multi-centric lobular carcinoma in situ. There was a questionable component of invasive carcinoma. The axillary node dissection revealed no evidence of metastases.

History revealed a recent diagnoses of "Chronic Fatigue Syndrome" and extreme allergies in the past year. This included allergic reactions to formaldehyde, fabrics and many new synthetic substances. She denied being diagnosed with CVD and blood tests were apparently negative.

Physical exam revealed three incisions in her left breast. One periareolar, horizontal in the inferior medial quadrant and in the left axilla. There were no abnormalities other than induration at the incision sites.

Because of the possible foci of invasive disease, external beam irradiation to the entire breast with a boost to the tumor bed was recommended.

She was treated with 6 MeV photons utilizing medial and lateral tangents to the left breast. Thirty degree wedges were used and computer planning confirmed a homogenous dose distribution. Field size was 16.4 x 20.8 cm. A daily dose of 180 cGy with a total dose of 5040 cGy was prescribed.

Signs and symptoms early in the treatment (900 cGy) with breast erythema, tenderness and constitutional symptoms with extreme fatigue, prompted us to pursue a detailed information regarding chronic fatigue syndrome.

Because of the severity of her symptoms, we performed additional testing. An antinuclear antibody and rheumatoid factor were negative, however, the erythrocyte sedimentation rate (ESR) was 49 (with normal being 0-20) and the antibodies to double stranded DNA with Farr assay (anti DNA-FARR) of 89 u/ml (normal 0-3.5u/ml) is highly indicative of SLE. Following a one week treatment break, persistent moist desquamation in the upper outer quadrant of the left breast and inframammary fold was noted. Erythema around the areola and inner quadrants had improved. Because of the severe reaction and diagnosis of SLE, it was recommended that radiation therapy be terminated at 3780 cGy and close follow-up with evaluation every three months during the first year and mammography every six months.

She returned one month later with significant improvement in the irradiated site with a small area of moist desquamation and persistent hyperpigmentation and moderate erythema (Figure 1).

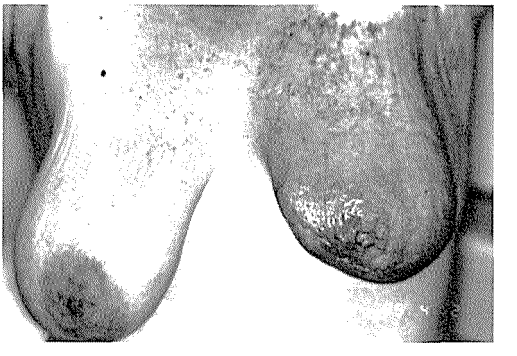

Figure 1. Area of moist desquamation and persistent hyperpigmentation and moderate erythema two weeks following 3780 cGy to the left breast.

Discussion

Systemic lupus erythematosus (SLE), a chronic inflammatory disease, appears to result from an immunoregulatory disturbance brought about by the interplay of genetic, hormonal, and environmental factors.[2] It is a disease of unknown etiology in which tissues and cells are damaged by deposition of pathogenic autoantibodies and immune complexes. Ninety percent of cases are in women, usually of child-bearing age, but children, men and the elderly can be affected.[3] Patients with SLE typically have disease that affects multiple organ systems. Not all systems, however, are involved simultaneously. The characteristic clinical course is one of exacerbations and remissions, the lat-

ter often lasting for many years. Criteria for classification of SLE were revised in 1982.[4]

This discussion is not centered around the diagnoses of SLE but, the suspicion of this disease in regards to radiation therapy and the appropriate course of action should the disease be determined during treatment.

Wallach describes two cases of lupus-like syndrome developing after therapeutic irradiation for locally advanced carcinoma of the breast.[5] This was characterized by pleuritis, pneumonitis, positive fluorescent antinuclear antibody reaction and lupus erythematosus preparation. Both patients responded to Prednisone for an extended period of time and had no evidence of radiation related disease or tumor progression. There were no abnormal acute treatment reactions noted in the article. The first patient was treated with 5000 cGy to the breast with a 2000 cGy boost to the mass. The second patient was treated with 3900 cGy to the breast, supraclavicular and axillary areas. Both patients had a history of non-deforming arthritis involving the hands, wrists, knees and ankles. It was proposed that radiation may have initiated an immunologic response leading to full blown SLE. Pleural effusions, pericarditis, or sever respiratory distress may have been induced from a lupus-like syndrome rather than a metastatic tumor radiation-induced disease.

Ransom *et al.*, discusses a case presentation of a 55 year old with scleroderma.[6] The patient received 45 Gy in 25 fractions to the breast, 45 Gy in 20 fractions to the supraclavicular fossa and apex of the axilla and 40 Gy in 25 fractions to the internal mammary chain. In addition, the tumor bed received 25 Gy in 54 hours by Iridium implant. No unusual acute skin reaction was noted. Three months following radiation, unusual induration developed and rapidly proceed to dense fibrosis in the treated area. In one year the shoulder movement was limited to a few degrees, there was marked arm edema and severe retraction and fibrosis of the breast. They conclude that the unusual reaction was caused by an unusual reaction of scleroderma with radiation.

Olivotto *et al.*, present a case report of a 25 year old woman with SLE who suffered fatal pelvic necrosis two years following radiation for carcinoma of the cervix.[7] An autopsy revealed no evidence of a residual tumor. There was pelvic ischemic necrosis with extensive pelvic fibrosis and fistulization. She was treated with three intracavitary tandem and ovoids. Point A received 1680 cGy with each insertion. The total rectal dose was 3830 cGy. This was followed with 40 Gy in 20 fractions with 10 MV photons with AP/PA fields and a 5 cm midline block. There were no technical difficulties with the insertion and minimal morbidity. They reviewed 158 consecutive patients with invasive carcinomas of the cervix and there were no increases in complications. They believed the endarteritis of SLE was either aggravated by or potentiated the effects of radiation leading to progressive pelvic fibrosis and necrosis. They believe that patients with connective tissue diseases do not tolerate radiation well.

Fleck *et al.*, retrospectively reviewed 5682 patients from 1959-1985 and discovered nine cases with CVD.[8] All patients received 40-50 Gy in the intact breast or chest wall at 1.8 to 2 Gy with boosts of five to 15 Gy at standard fractionation. Of these nine patients, five underwent breast conservation. Five of the nine patients received chemotherapy, three before irradiation and two after irradiation. Four of the patients had known pre-existing CVD prior to radiation and three of them developed exaggerated acute and late effects within two years of treatment. The five women who developed CVD three months to ten years following treatment had no complications. Of the four patients with pre-existing CVD, two were specifically diagnosed with SLE. One suffered moist desquamation, lymph edema of the arm, flap necrosis, severe lung damage, a bronchopleural-cuta-

neous fistula and osteoradionecrosis of the clavicle, sternum and rib cage. The authors conclude that pre-existing CVD appears to represent a relative contraindication for any elective high or moderate-dose radiation therapy.

Robertson *et al.*, reports two cases of CVD which exhibit extremely poor cosmetic results.[9] One patient had scleroderma and the second rheumatoid arthritis (RA). The first patient (RA) received 5251 cGy at 210 cGy fractions followed by a 1600 cGy iridium-192 implant boost. She exhibited no unusual acute reactions, however, 11 months post treatment she developed breast swelling, erythema and severe pain. The breast was hard, fibrotic and fixed to the chest wall. The appearance was similar to an inflammatory carcinoma. However, a simple mastectomy revealed no malignancy. Two years following the mastectomy she remains free of recurrence and her chest wall is symptom free, however, her RA has progressed. The second patient (scleroderma) received 5040 cGy in 180 cGy fractions to her left breast, supraclavicular region and a posterior axillary boost. During treatment, she developed a brisk skin reaction and worsening of skin and joint symptoms. A diagnosis of scleroderma was made six months following therapy. At 16 months the breast was severely fibrotic and retracted. There were also rib fractures in the treatment field. They concluded that both patients exhibited an acceleration of systemic disease either during RT or shortly thereafter. They believe that CVD must be active before or during RT for severe fibrosis and severe late injury to occur.

Varga *et al.*, presents four patients with systemic sclerosis (SSc).[10] Two of the patients had breast cancer. The first patient was a 38 year old status post MRM who received 50 Gy to the chest wall and draining nodes followed by adjuvant chemotherapy (CMF). Two months following RT she developed Raynauds phenomenon and swelling of the hands with subsequent increasing skin tightness. She had a right hip metastasis treated four years following this with 40 Gy in 2.5 Gy fractions. She developed an extreme fibrotic reaction in the treatment area within four months of treatment and subsequently developed small bowel obstruction (SBO). She died two years following her second course of radiation. The second patient with invasive ductal adenocarcinoma of the right breast underwent a radical mastectomy followed by RT and CMF chemotherapy. She received a 9 MeV electron beam with 20 Gy at 1 cm depth in 25 fractions through a 10 x 10 cm field. Three months following RT she noted swelling of the right hand, forearm, and arm. During the next three months she developed rapidly progressive asymmetrical skin induration and thickening involving the right arm and right side of her trunk and contracture of the fingers of the right hand. The authors concluded that the areas of radiation induced fibrosis extended well beyond the confines of the radiation portals. Three of the four patients died of complications of the fibrotic process without evidence of recurrent malignant neoplasms. They concluded some patients with SSc develop a markedly exaggerated fibrotic response following localized ionizing radiation. Caution should be used in the delivery of RT to patients with SSc.

Ross *et al.*, has the largest published data base to date.[11] They presented a retrospective review of 61 patients with CVD compared to a matched control group. The patient distribution was as follows: 39 RA, 13 SLE, 4 SSc 4 dermatomyositis (DM) and one with polymyositis (PM). They concluded overall no significant difference between the CVD and control group in terms of acute or late complications. Of this group, three patients suffered fatal complications and they all resided within the CVD group. Of the three fatalities, one had SLE with uterine sarcoma and subsequent radiation induced bowel necrosis.

Another had RA with infiltrating ductal carcinoma of the left breast and died of chronic pericarditis secondary to radiation therapy. There was also one difference in the incidence of late complications compared to none in the control group. They found the highest incidence of normal tissue damage were those in whom CVD was diagnosed after radiation therapy. This occurred in four of six patients. SLE patients had a higher rate of acute reactions while late complications were actually less in this group. They are clear in pointing out that the three fatal complications are not significant and that two of the complications occurred in patients with excessive doses that would cause a high risk of late complications anyway. They found no statistically significant increase of complications in those with CVD diagnosed prior to therapy compared to those diagnosed following therapy. Their conclusion is that although there is no reason to withhold radiation treatment to individuals with CVD, it would be prudent to be cautious in the treatment of these individuals until more studies have been reported.

Strober *et al.* present an uncontrolled feasibility study to support the use of total lymphoid irradiation for the treatment of intractable lupus nephritis.[12] All patients had a diagnosis of SLE, histopathologic evidence of lupus nephritis involving more than 85% of the glomeruli and failure to respond to Prednisone therapy. Ten patients were subsequently treated with 6 MeV photons. The mantle field utilized 2000 cGy in 200 cGy fractions five days per week. The subdiaphragmatic field received 2000 cGy in 150-200 cGy fractions and differing techniques for males and females of child bearing age were utilized. The kidneys were not irradiated in any instance. This study showed that total lymphoid irradiation may be an alternative to cytotoxic drugs in the treatment of lupus nephritis. Extrarenal manifestations of lupus nephritis, including skin rash, headaches, myalgia, arthralgia, ect were present in nine of the ten patients prior to RT and absent or minimal in all at last observation.

Teo *et al.*[13] retrospectively reviewed 1154 patients treated for nasopharyngeal carcinomas (NPC) from 1976-1986. Of this group, 10 patients were found to have dermatomyositis (DM). All but one patient had DM prior to RT. Two of the ten patients developed severe radiotherapy complications (skin necrosis) and all ten exhibited subcutaneous indurated fibrosis affecting both sides of the neck. Because of this response, they recommend avoidance of elective cervical irradiation in node negative NPC with CM.

Conclusion

The purpose of this report was to present potential concerns when SLE is diagnosed during radiation treatment to the breast. The largest study to date by Ross *et al.*, had 61 patients with a matched control group and showed no statistical differences in acute or late effects overall, but side effects were increased in breast cancer patients.[11] In this study there were 13 patients with SLE. The remainder or the literature deals with limited case reports. The patient presented here did indeed have a significant and extreme acute reaction to radiation. We recommend a diligent search for SLE or other CVD if the patient experiences an unusually extreme acute reaction. It is also clear that in this case it was beneficial to repeat tests and to utilize more specific tests based upon clinical suspicion. It is still too early to determine what possible late effects will develop in this patient. The proper dose and fraction size is not known in treating individuals with SLE.[7] There are a very small number of patients treated with radiation therapy who have SLE and it is clear a randomized trial is not feasible. If a patient experiences severe acute side

effects in the first week of radiation, consideration should be given to SLE testing. If SLE is diagnosed, radiation therapy should be discontinued and further surgery recommended. Mastectomy represents an equally efficacious treatment and each patient should be given this alternative and apprised of the possible increased risk of side effects associated with radiation and CVD.

References

1. Harris JR, Morrow M, Bonadonna G. *Cancer of the breast. Cancer principles and practice of oncology.* 4th Ed. Philadelphia: JB Lippincott Company 1993. p. 1280-7.

2. Alarcon-Segovia D. The pathogenesis of immune dysregulation in Systemic Lupus Erythematosus: A troika. *J Rheumatol* 1984; **11:** 588-90.

3. Schumacher HR, Klippel JH, Robinson DR. Primer on the rheumatic diseases. 9th Ed. Georgia: Arthritis Foundation; 1988. p. 96-111.

4. Hahn BH. Systemic Lupus Erythematosus. In: Wilson JD, Braunwald E, Isselbacher KJ, Petersfdorf RG, Martin JB, Fauci AS, Root RK. Harrison's eds. *Principle of internal medicine.* 12th Ed. New York: McGraw-Hill; 1991. p. 1432-7.

5. Wallach HW. Lupus-like syndrome associated with carcinoma of the breast. *Arch Intern Med* 1977; **137:** 532-5.

6. Ransom DT, Cameron FG. Scleroderma - A possible contra- indication to lumpectomy and radiotherapy in breast carcinoma. *Australasian Radiology* 1987; **31:** 317-8.

7. Olivotto IA, Fairey RN, Gillies JH, Stein H. Fatal outcome of pelvic radiotherapy for carcinoma of the cervix in a patient with Systemic Lupus Erythematosus. *Clinical Oncology* 1989; **40:** 83-8.

8. Fleck R, McNeese MD, Ellerbroek NA, Hunter TA, Holmes FA. Consequences of breast irradiation in patients with pre-existing collagen vascular diseases. *Int J. Radiat Oncol Biol Phys* 1989; 829-33.

9. Robertson JM, Clarke DH, Pevzner MM, Matter RC. Breast conservation therapy: Severe breast fibrosis after radiation therapy in patients with collagen vascular disease. *Cancer* 1991; **68:** 502-8.

10. Varga J. Haustein UF, Creech RH, Dwyer JP, Jimenez SA. Exaggerated radiation- induced fibrosis in patients with systemic sclerosis. *JAMA* 1991; **265:** 3292-5.

11. Ross JG, Hussey DH, Mayr NA, Davis CS. Acute and late reactions to radiation therapy in patients with collagen vascular diseases. *Cancer* 1993; **71:** 3744-52.

12. Strober S, Field E, Hoppe RT, Kotzin BL, Shemesh O, Engleman E. Ross JC, Myers BD. Treatment of intractable lupus nephritis with total lymphoid irradiation. *Ann Intern Med* 1985; **102:** 450-8.

13. Teo P, Tai TH, Choy D. Nasopharyngeal carcinoma with dermatomyositis. *Int J Radiat Oncol Biol Phys* 1989; **16:** 471-4.