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Correspondence and Short Communications

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SKIN INFILTRATION WITHIN A RADIOTHERAPY PORTAL FOR METASTATIC BLADDER CANCER—CASE REPORT AND REVIEW OF THE CLINICAL LITERATURE

Since its first description in 1935, there have been occasional reports of skin infiltration by tumour in a distribution corresponding to previous radiation portals (1–7). Attempts to explain the phenomenon have invoked local capillary endothelial damage and immunological or physiological changes secondary to radiation (8–10). Whilst generally associated with biologically aggressive tumours and poor prognosis, it is unknown what predisposes a small proportion of such tumours to display this complication of radiotherapy (RT). We now describe a case of skin infiltration following left neck irradiation for nodal metastases from transitional cell carcinoma of the bladder and review the clinical literature on this effect.

Case report. A 75-year-old male Jehovah's Witness with a 6-month history of haematuria had a cystoscopic resection in December 1990 of a solitary grade II transitional cell carcinoma showing superficial bladder muscle invasion. Complete blood picture, multiple biochemical analysis, chest x-ray and CT scan of abdomen and pelvis were negative for metastatic disease, and the tumour was staged as T2 N0 M0 (11). Surgery was considered inadvisable due to his age and refusal to consider blood transfusion, and he was referred for RT, receiving 52.2 Gy to pelvis with a 12.6 Gy boost to bladder, 36 fractions at 1.80 Gy/fraction, completing treatment in April 1991.

He remained well with negative check cystoscopies in July and November 1991, at which time he was noted to have several asymptomatic left supraclavicular nodes, the largest about 1.5 cm in diameter. Fine-needle aspiration cytology of the nodes was positive for undifferentiated carcinoma, presumed from the bladder primary. In the absence of obvious metastatic disease elsewhere on physical examination, blood tests, and chest x-ray, the decision was taken to treat the left neck with RT. From late December 1991, he had 45 Gy in 15 fractions at 3 Gy/fraction, 5 times per week, using an anterior 15 × 11 cm 4 MV photon field at D_{max} with 1 cm bolus to the nodes (requiring a 10-day break after 24 Gy due to severe radiation oesophagitis), followed by two 6 MeV electron boosts, 6 Gy D_{max} in 2 fractions to a 6 cm diameter circle and 3 Gy D_{max} in 1 fraction to a 4 cm diameter circle, over a total of 35 days. Skin reaction was limited to brisk erythema with dry desquamation, and treatment was finished in early February 1992.

A few weeks later, he started developing pain in his left shoulder and left upper limb suggestive of brachial plexus involvement, and noted a patch of purplish skin in the left supraclavicular fossa. By June 1992 (5 months after completing RT), there was a diffuse, nodular violaceous tumour with well demarcated borders outlining the previous radiation field over a 14 × 10 cm area with maximum thickness above surrounding skin of about 1 cm (Figure). Left shoulder movements were limited due to pain, the left biceps and triceps jerks were diminished, and there was mildly decreased pin prick sensation in the left C6 distribution. His general condition had deteriorated significantly, with anorexia and 4 kg weight loss. Fine-needle aspiration biopsy of the infiltrating tumour was reported as consistent with poorly differentiated metastatic transitional cell carcinoma. Limited re-staging revealed mild elevation of alkaline phosphatase and lactate dehydrogenase, normal complete blood picture and chest x-ray. Whole body bone scan (performed mainly to exclude bone metastases as the source of his pain), confirmed multiple metastases, although none in the cervical spine, left shoulder or left upper limb regions. Cystoscopy was not repeated as he had no significant urinary symptoms.

He was offered palliative chemotherapy with a view to reducing his narcotic requirements and delaying skin ulceration/fungation. Single agent cis-platinum 70 mg/m^2 was used, due to the likely need for transfusion with a more myelosuppressive regimen, but was poorly tolerated (vomiting and lethargy), and he refused futher chemotherapy. On review in August 1992, $3\frac{1}{2}$ weeks later, there was marked response in the left neck, with flattening of the lesion and reduction in pain. However, by September 1992 there had been significant regrowth extending beyond the originally irradiated region, and he was offered further RT to palliate pain and hyperaesthesia (his prognosis being so poor that late toxicity was unlikely to be an issue). This consisted of several 2–3 fraction courses of photons and electrons at 3 Gy/fraction, to which there was temporary response, but inexorable rapid regrowth of the lesion. He also required RT to the left femur for bone pain, and left axilla due to a tender nodal mass. He died from a presumed pulmonary embolus in November 1992, 8 months after first developing the skin infiltration.

Discussion. Although experienced radiation oncologists anecdotally report occasional skin relapse of tumour confined to a previosly irradiated region, there is little documentation of this phenomenon in the literature. The first 2 cases were described in 1935, one in a posterior portal following bypass surgery, RT (total dose 24 Gy), then gastric resection for carcinoma of the stomach, onset 15 months after RT, the second following radical mastectomy and adjuvant parasternal, chest and axillary irradiation (total dose 15 Gy) for breast carcinoma, onset 9 months after RT (1, 2). Eight other cases have been reported following mastectomy and adjuvant loco-regional RT (31–55 at 2.0–2.2 Gy/fraction where stated), with delays ranging from 3 months to 4 years and 3 months after RT (3–5). Clinical photographs of 4 post-mastectomy cases have also been presented with limited histories. Intervals between irradiation and appearance of skin deposits were 6, 7, 9 and 18 months (7, 8). Twelve similar cases were recorded in a single large centre during routine follow-up of breast

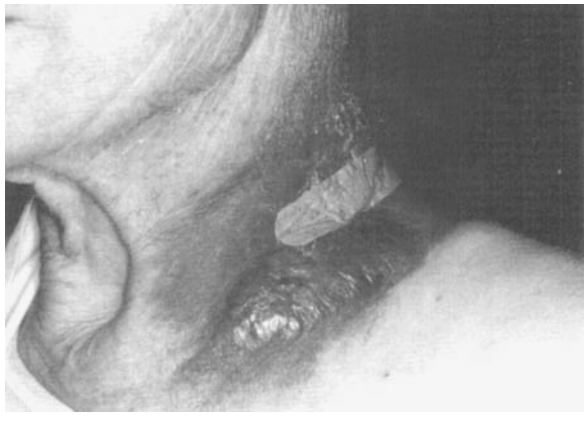

Figure. Skin infiltration in the left neck confined within radiotherapy portals given 5 months previously.

cancer patients within one year, but no details were given (8). A retrospective review reported in abstract form implicated adjuvant RT in chest wall (and pleuro-pulmonary) relapse for breast cancer patients treated initially by surgery. There was a 30.5% (46/150) incidence of 'cuirasse syndrome' in irradiated patients compared with only 11% (11/100) in non-irradiated ones ($p < 0.001$), despite 'comparable primary tumour characteristics and initial loco-regional extension'. However, it is impossible to interpret these (unusually high) recurrence rates without further clinical details, and the authors were presumably not referring to the well-demarcated pattern of infiltration under present consideration (12).

Other non-breast primary tumours have also rarely demonstrated this phenomen. Meltzer et al. (6) described tumour developing in the anterior supraclavicular and mediastinal portal used for a low neck recurrence of squamous cell carcinoma of the nasopharynx 23 months after the start of a course of 60 Gy at 2 Gy/fraction to the region. Dao & Moore (4) reported skin infiltration in the abdominal portal 10 months after RT for presumed recurrence of a uterine cancer, which had initially been treated with intracavitary and external beam lower abdominal irradiation 32 months prior to the skin involvement.

The only other reference we could find in relation to bladder cancer was from Japan where an 85-year-old male developed lower abdominal skin infiltration following two courses of pelvic RT. Twenty Gy at 2 Gy/fraction had been given before cystoscopic resection of multiple transitional cell carcinomas $2\frac{1}{2}$ years previously, and a further 50 Gy (fractionation not stated) when pelvic nodal recurrence occurred. The second course preceded the development of skin nodules by 1 month. However, it was not explicitly stated that the infiltration was confined to the RT portals (13).

The pathogenesis of this and other metastatic phenomena in relation to RT generated considerable research interest in the 1960's and 1970's when animal experiments suggested irradiation of lung, kidney, and liver predisposed to the subsequent development of secondary deposits (14–16). There was experimental support for the concept of tumour cell 'trapping' in capillaries whose endothelial cells had been damaged by irradiation (9). Other workers have emphasized the possible contribution of RT to impairment in immune mechanisms (8), change in the 'physiological microenvironment' (10), or abnormalities in paracrine growth factors (12).

Despite these findings, data have generally not supported the enhancement of metastasis by radiotherapy in the clinical context. The well-established role of adjuvant RT in combined modality regimens to improve local control and/or survival in many malignancies provides strong evidence against this.

What then accounts for rare cases like those described above? It certainly does not appear to depend upon excessive skin dose, most instances occurring after conventional fractionation schedules. Review of the cases described above reveals no obvious association with beam quality (orthovoltage versus megavoltage) or type (photons versus electrons), nor with gender, age (range 37–85), or hormone dependence of the tumour. On the other hand, all instances have been restricted to the trunk or low neck (in continuity). The case reported by Meltzer et al. (6) is interesting in this respect. Despite 60–70 Gy in 6–7 weeks to the nasopharynx and upper to mid-neck at presentation, and a further 40 Gy (details not given) to a retro-orbital recurrence 22 months after the start of RT for low neck recurrence (described above), the skin infiltration commencing a month later was confined to the low neck and mediastinal portal, and did not involve the head at all.

Another interesting observation, at least in the reported breast series, is the consistently poor prognostic features at initial presentation. Of Cole and Halnan's four cases three were node-positive, one axilla 'massively invaded', one breast having 'multiple foci of invasion', and the fourth had an 'enlarged reddened' breast with lymphatic and vascular permeation (3). Dao and Moore's two breast cases (4) had respectively 6 of 11 involved nodes, and a 10×7 cm axillary mass, while those of Diehl et al. (5) had 35 of 35 and 22 of 22 positive nodes, one with poorly differentiated histology.

It is also clear that the skin infiltration generally is related temporally to the development of other regional and systemic metastases, with limited survival thereafter. In two of Cole and Halnan's breast cancer patients disseminated disease was detected 6 and 9 months after the skin involvement, with survivals of 7 and 18 months respectively (3). Corresponding figures from Diehl et al. (5) were less than 1 and 4 months, with survival of 5 and 8 months. One of Dao and Moore's breast cases developed a synchronous contralateral breast mass at the time of the skin infiltration, the other had an ipsilateral supraclavicular recurrence 7 months before this occurred (4). There were 3 regional relapses in the nasopharyngeal carcinoma patient, occurring 23 months (neck), 15 months (neck) and 1 month (orbit) prior to the dermal involvement (6). With the two bladder cases, distant metastases (axillary and cervical nodes respectively) preceded the skin manifestations by about 3 months in both patients (13, current).

Response of the skin infiltration to treatment appears to be uncommon. Of the 8 breast carcinoma cases described in detail, two patients responded to hormonal manipulation and one of these had a further response to single agent cyclophosphamide. There was no response in 4 other breast patients to oophorectomy, adrenalectomy, doxorubicin + vincristine + tamoxifen, and doxorubicin + vincristine followed by mitomycin C + BCNU + tamoxifen then interferon respectively. Follow-up data was not available for the remaining two (3–5). The skin infiltration in the uterine carcinoma case progressed rapidly after administration of cortisone (4), treatment was apparently not attempted for the nasopharyngeal carcinoma patient (6), was refused by the bladder cancer patient from Japan (13), but chemotherapy, and then further RT were of temporary benefit in the current report.

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DNA CONTENT—A PROGNOSTIC FACTOR IN CHILDHOOD MEDULLOBLASTOMA?

The treatment results in pediatric brain tumors, especially medulloblastoma, still lags behind the remarkable positive achievements obtained in most other types of childhood cancers. Based on some encouraging results from CCSG and SIOP studies, a treatment modality consisting of combined chemotherapy, surgery and irradiation has been introduced for the treatment of highly malignant brain tumors, replacing the traditional approach of surgery and irradiation (1, 2). Very aggressive chemotherapy followed by bone marrow rescue has also been suggested for advanced cases. Identification of the parameters related to the prognosis is important for deciding on the intensity of chemotherapy to be used. Prognostic significance has been reported for several histologic and clinical features, i.e. tumor size and extent, CSF cytology, age at diagnosis and extent of resection (3). Predicting the outcome, based on these parameters, is still rather uncertain, and therefore the search for additional prognositc variables is ongoing. DNA content is known to be a valuable prognostic factor in acute leukemia and neuroblastoma (3). Studies of tumor cell DNA content have suggested that DNA aneuploidy and conversely DNA diploidy may be favorable features in medulloblastoma (4, 5). Schofield et al. (6) have recently reconfirmed DNA aneuploidy to be a relatively favorable factor in medulloblastoma, especially amongst patients with a disseminated disease at the time of diagnosis.

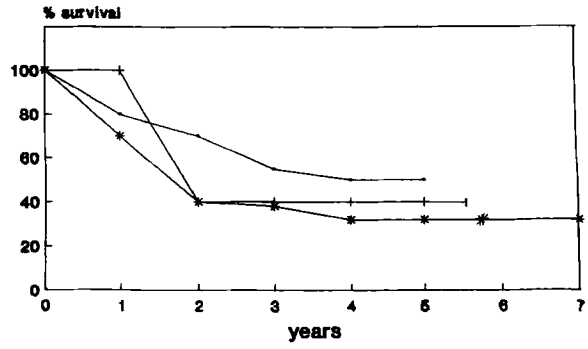

Figure. Patient survival according to DNA pattern of the tumor. —•— Tetraploid (n = 5); —|— aneuploid (n = 5); —*— diploid (n = 11).

Twenty-six patients with medulloblastoma, who were treated at the Sheba Medical Center between 1982 and 1990, were studied. Median age was 5 years. Therapy consisted of radical surgical resection, radiotherapy and chemotherapy according to Pendegrass et al. (7). Using the technique described by Hedley et al. (8). We analysed cells from paraffin-embedded pathological blocks and estimated the DNA content by flow cytometry (FACS). Three sections were cut from each block to reduce sample error. Adequate tissue for DNA content analysis was available in 21 cases only.

Our results showed no statistically significant differences between survival in the three groups of DNA ploidy (diploidy, aneuploidy, tetraploidy) according to the Mantle-Cox-test (Figure). The three groups were similar concerning age, tumor size and extent, degree of resection, and therapy.

Our results were thus disappointing but there seems to be a lack of consistency between different studies concerning the role of DNA content as prognostic factor in pediatric medulloblastoma. We feel that further extensive studies are required to elucidate the possible association between DNA pattern and prognosis and before it can be used as a guide for the choice of therapy.

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