Irradiation-induced penile angiosarcoma

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Summary: We report a case of angiosarcoma of the glans penis in a 77 year old male Caucasian. The tumour developed 18 years after a course of radiotherapy for a penile ulcer which was an intra-epidermal squamous carcinoma. The differential diagnosis and the concept of radiotherapy-induced angiosarcomas are discussed.

Introduction

Angiosarcomas of the skin and soft tissues are well described malignancies which usually involve specific sites, namely the scalp and face, lympho-oedematous extremities and the breast. A small sub-category of angiosarcomas arising in previously irradiated sites has been sparsely documented. These tumours may present decades after the initial radiation exposure.

Primary mesenchymal tumours of the penis are rare. Squamous cell carcinomas and metastatic deposits have a much higher incidence. Since 1950, 12 cases of primary penile angiosarcomas have been found in the literature.

Most of the patients were in the 5th, 6th and 7th decades, the youngest case being 17 years old. The commonest initial presenting symptoms were penile pain, priapism, swelling, and painless haematuria; all were usually associated with a visible ulcer or tumour mass.

The treatment instituted was a combination of radiotherapy and local/radical amputation. Chemotherapy was given to patients with disseminated disease. The mean survival time was 13.8 months (range: 10–22 months) although 2 cases have survived 15 years since diagnosis.^{1,2} One case had previous exposure to vinyl chloride³ and another had a history of previous trauma.⁴ None of the cases had prior radiation exposure, as in the patient presented here.

Case report

A 77 year old male Caucasian presented in 1970 with a sore on his glans penis. He had previously been well. A biopsy of the ulcer was diagnosed as intra-epidermal squamous carcinoma. A course of

radiotherapy consisting of 800 rads single exposure was instituted and the lesion regressed clinically, although some radionecrosis was noted even up to 5 years later.

Regular follow-ups showed no sign of recurrence until 1988, when he presented with a large, fungating, cauliflower-like growth involving most of his glans penis which bled easily on contact. He did not have any inguinal lymphadenopathy or systemic signs of disseminated malignancy.

In view of his previous lesion, this growth was regarded as a recurrence of the initial squamous carcinoma and he therefore underwent penile amputation with a perineal end urethrostomy. At operation, the tumour had invaded the corpora cavernosa and the urethra as far as the proximal penile shaft.

He died 4 months later and a post-mortem revealed disseminated tumour in both lungs and liver. The root of the penis contained residual tumour and there were inguinal and pelvic lymph node metastases.

Our patient did not have any symptoms or signs of the AIDS complex and he was human immunodeficiency virus negative to the best of our knowledge.

Pathology

Gross

The specimen consisted of a distorted glans penis with shaft, together measuring 9 cm in length, the shaft diameter being 4 cm. The glans was totally replaced by a huge, fungating, tumour mass measuring 7 × 6 × 3 cm, whose surface was partially ulcerated and haemorrhagic. A pinpoint external meatus was identified. The prepuce was also involved by this tumour. The deep margin of the tumour had an ill-defined, infiltrative edge. In addition, there were several separate, circum-

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scribed satellite tumour nodules in the corpora cavernosa measuring up to 2 cm in maximum diameter. One such nodule extended to within 0.5 cm of the proximal resection margin.

Histology

The tumour exhibited extensive areas of neoplastic vessel formation with intercommunicating channels lined by plump or flattened endothelial cells (Figure 1). These cells showed cellular and nuclear pleomorphism, large nuclei with prominent nucleoli and numerous mitotic figures some of which were aberrant.

In addition there were solid cellular areas composed of spindle cells whose nuclei had similar cytological features to the neoplastic endothelial

cells. The satellite nodules in the shaft showed infiltration of the surrounding tissues. There was a sparse lymphocytic reaction to the tumour. Reticulin stains outlined the vascular channels and demonstrated beyond reasonable doubt that the tumour cells were within these channels.

Immunohistochemical staining of Factor 8 Rag and the plant lectin Ulex Europaeus 1 (UEA-1), both recognized markers of vascular endothelium, showed definite cytoplasmic positivity of some of the cells within the neoplastic vessels (Figure 2). The solid, undifferentiated spindle cell areas showed irregular, patchy cytoplasmic positivity.

Ultrastructural examination revealed incomplete basal laminae surrounding the primitive neoplastic vessels. The cells contained irregular nuclei with multiple invaginations and prominent

Figure 1 Histology of tumour demonstrating neoplastic intercommunicating vascular channels (H&E, Obj $\times$ 120).

Figure 2 Section stained with Ulex Europaeus lectin. The arrows demonstrate the positive cytoplasmic staining of some cells (Avidin-biotin technique, Obj $\times$ 120).

nucleoli. Micropinocytic vesicles were seen in the cytoplasm and primitive tight junctions were present between the cells. No microtubular rod shaped bodies (Weibel-Palade bodies) were identified.

Discussion

The main differential diagnosis lies between haemangiosarcoma and Kaposi's sarcoma. Histologically, the most prominent feature seen in our case was the neoplastic vascular proliferation. Although similar areas can be seen to a lesser extent in Kaposi's sarcoma, they are usually situated in the periphery of the tumour nodules. Also, the spindle cell areas of classical nodular Kaposi's sarcoma show slit-like spaces filled with erythrocytes. This important feature was absent in our case.

The use of Factor 8 Rag and the more sensitive but less specific Ulex Europaeus 1 markers are reliable in confirming vascular origin in a given tumour. However, these markers cannot convincingly distinguish between angiosarcoma and Kaposi's sarcoma, the results of various studies being variable and controversial.⁵⁻⁸

Our ultrastructural findings are consistent with a malignant vasoformative tumour. There were no features of epithelial (i.e. desmosomes, tonofilaments) or other specific mesenchymal differentiation. The absence of Weibel-Palade bodies, pathognomonic for vascular endothelium, is disappointing but they are only present in a small percentage of anaplastic angiosarcomas.⁹

An important ultrastructural feature in Kaposi's sarcoma is erythrophagocytosis by the neoplastic cells. This leads to the formation of erythrophagosomes, erythrophagolysosomes, myelinosomes, myelinosiderosomes and siderosomes.⁹ Our case did not show any of these readily identifiable structures. In summary, the combined histological immunohistochemical and ultrastructural findings support the preferred diagnosis of angiosarcoma rather than Kaposi's sarcoma.

Previous studies in grading angiosarcoma according to growth patterns, mitotic activity or cytological features have failed to show good correlation with survival. However, small tumour size (less than 5 cm) and a marked lymphocytic response are reported as features associated with prolonged survival.¹⁰

The aetiological factors implicated in angiosar-

comas include chronic lymphoedema, radiation and exposure to environmental carcinogens, in particular, thorium dioxide (Thorotrast), arsenic-related compounds and vinyl chloride. The latter has been implicated with hepatic angiosarcomas. Ghandur-Mnaymneh and Gonzalez³ speculated on the role played by vinyl chloride in the oncogenesis of penile angiosarcoma but no definite association was concluded. Trauma was incriminated by Kovacs *et al.*⁴ as a predisposing factor in penile angiosarcoma but the evidence remains equivocal in spite of other reports.¹¹

Radiation-induced angiosarcomas have been well described entities since Perthes' report¹² in 1904. Five of the 44 cases reported by Maddox and Evans,¹⁰ 2 of the 44 cases reported by Sordillo *et al.*,¹³ and other reports¹⁴⁻¹⁸ attest to the fact that radiation *per se* may lead to the development of angiosarcomas. To be classed as such, these angiosarcomas must arise within the radiation field after an interval of several years, and they must not be associated with chronic lymphoedema. Those which follow radiation for genitourinary malignancies usually develop on the lower abdominal wall.

The time interval between the radiation exposure and diagnosis has been reported as approximately 12 years by some workers^{10,15} and between 8 to 42 years (mean 17.5) by others.¹⁴ The dose of external irradiation ranged from 2,400 to 6,000 rads in total in one series.¹⁴

The radiation dosage in this case is low compared with other studies but skin angiosarcomas have been reported following low dose irradiation for benign conditions such as eczema.¹⁵

These observations support a cause-and-effect relationship between irradiation and angiosarcomas. Apart from the direct carcinogenic effect of irradiation, it is thought that prolonged tissue repair stimulation due to irradiation-induced tissue ischaemia plays a pathogenetic role.

Our case illustrates the need to bear in mind this infrequently documented but well recognized complication of radiotherapy and to the best of our knowledge is the first case to be reported at this site.

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