

The response of adenoid cystic carcinoma to tamoxifen

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Abstract

Adenoid cystic carcinoma of the parotid gland often recurs locally, or metastases develop, after initial treatment with surgery and radiotherapy. We report a patient with an inoperable local recurrence of previously irradiated adenoid cystic carcinoma, who was treated with tamoxifen, an oestrogen receptor antagonist.

After 18 months of treatment with tamoxifen, MRI showed a partial response, and further clinical progression of the disease was halted.

Key words: Parotid neoplasms; Carcinoma, adenoid cystic; Tamoxifen

Introduction

Adenoid cystic carcinoma (ACC), arises most often in the salivary glands, but it can also arise in other sites such as breast, skin, ear canal, lacrimal gland, prostate, lung, and uterine cervix (Leafstedt *et al.*, 1971). Radical surgery and radiotherapy usually produce initial local control but the tumour has a slow growth pattern and there is a tendency to recur after a period often up to 10 or 15 years, often with systemic metastases. Perineural spread means intracranial extension and is not uncommon. In a series from Manchester, patients treated by radiotherapy only after a biopsy achieved real tumour control in 37 per cent, which demonstrates the radioresponsiveness of this type of carcinoma. Despite local control, 43 per cent of patients with major salivary gland tumours died from metastatic disease (Cowie and Pointon, 1984). Tamoxifen is an oestrogen receptor antagonist widely used in the management of patients with breast cancer. Some salivary gland carcinomas have been shown to have oestrogen receptors (ER), progesterone receptors (PR) and some other oestrogen-induced protein (EIP) (Kolar *et al.*, 1994). A literature survey failed to reveal any other report of the use of tamoxifen in ACC of the salivary glands.

Case report

A 56-year-old female patient presented in September 1980 with a lump below her right ear. Local excision was performed and the histology was reported as showing pleomorphic salivary adenoma. In 1982, 21 months after initial surgery, she developed a mild right facial paresis which progressed to a complete right palsy over the following 10 months. Chest X-ray, computed tomography (CT) auditory meatus views and technetium 99m scan of the parotids all failed to reveal any abnormality. As review of the original histology from 1980 showed a definite poorly differentiated adenocarcinoma with a thin rim of residual salivary gland tissue, recurrent disease was strongly suspected on clinical grounds.

In view of this, pre- and post-operative radiotherapy was recommended. Pre-operatively she received 40 Gy in 12 fractions over 21 days to her right parotid. This was

followed in August 1983 by total parotidectomy and block dissection of the right neck. She made an uneventful post-operative recovery and the histology showed no evidence of tumour in the tissue removed or in the 13 identified lymph nodes. The planned post-operative radiotherapy was therefore not administered. Tarsorrhaphy and masseter slings for the drooping angle of her mouth were performed.

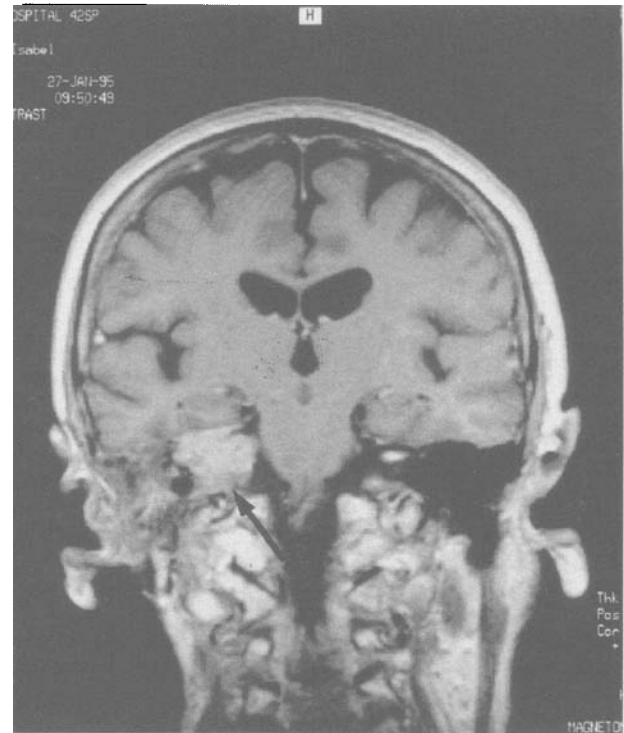
She was well until November 1984 when she started to experience increasing deafness in the right ear. Initially, after aural toilet, her symptoms disappeared. Pure tone audiometry suggested a conductive loss with reduced cochlear reserve, absent stapedial reflexes and increased compliance. Ossicular discontinuity was tentatively diagnosed. At right tympanotomy in January 1989 tumour was seen along the course of the facial nerve. She then underwent an extended mastoidectomy, at which the tumour was found to extend towards the petrous apex and complete excision was not possible. Histology from this specimen now confirmed the tumour to be an adenoid cystic carcinoma. She then received radical radiotherapy to the right temporal region. In all a further 48 Gy in 30 fractions was administered. She developed some vertigo and complete deafness in the right ear. Later osteoradionecrosis of the right external auditory canal became evident.

She remained well until January 1995 when she developed a tingling sensation in the right cheek and right side of the tongue. An MRI scan of the upper neck and parotid region showed extensive recurrent carcinoma extending into both the middle and posterior cranial fossa (Figures 1a and b). Chest X-ray showed no pulmonary metastases.

The consensus following multi-disciplinary consultation was that the malignancy itself was incurable and palliative support was to be provided. The patient found the 'no treatment option' unacceptable. In February 1995 tamoxifen 20 mg o.d. was recommended, on the basis of reports of oestrogen receptor positivity in a small proportion of patients with salivary gland neoplasms (Kolar *et al.*, 1994). The patient showed no subsequent clinical progression of



(a)



(b)

FIG. 1a, b

MRI scans showing extent of disease prior to treatment with tamoxifen.

her disease which was reassessed by MRI in July 1996, after 18 months of tamoxifen treatment. This showed very significant improvement (Figures 2a and b).

In view of this unexpectedly good result, the patient continued on tamoxifen. She was last seen on a routine clinic visit two weeks prior to her death (in December 1996) when she appeared well with no clinical evidence of tumour activity. Post-mortem examination was not performed.

Discussion

ACC originally termed a cylindroma by Bilioth in 1856 is also called basaloma, adenocystic or adenocystic carcinoma. It is an uncommon, slow growing tumour which may arise in both major and minor salivary glands. It accounts for less than five per cent of all parotid neoplasms, and 10 per cent of submandibular neoplasms. It is relatively more frequent among tumours arising in minor salivary glands of the upper aerodigestive tract.

Grossly it tends to have a uniformly grey, firm cut surface. These lesions are not encapsulated and also do not exhibit areas of haemorrhage and necrosis, unlike other malignant salivary gland tumours. They can be of a predominantly tubular pattern, or predominantly cribriform pattern, or a combination of both (Conley and Dingham, 1974). No significant difference in response to treatment is seen between the different histological types.

ACC may invade adjacent salivary gland tissue directly. These tumours frequently demonstrate intravascular, perineural and intraneural invasion. ACC in the parotid gland may cause pain by involvement of the facial nerve, the great auricular nerve or auricular temporal nerve. The ACCs which reach the base of the skull place all the cranial

nerves in jeopardy. ACC also frequently sends long tentacles of tumour between lobules of otherwise normal salivary gland tissue, so that tumour is found far beyond the area where the lesion is palpable. Local infiltration to bone and fascial planes also occurs. A tendency to recur locally after surgical excision with later regional and distant spread are all parts of its relentless growth characteristics (Perzin *et al.*, 1978).

The size of the primary tumour also affects prognosis, the larger the primary lesion, the worse the prognosis. Only five to seven per cent have regional metastases at the initial examination (Conley and Casler, 1991). Fifty-six per cent of ACC occurred in females and 44 per cent in males in a series by Conley and Dingham, 1974. Fine needle aspiration cytology has a 95 per cent accuracy rate in these tumours (Azumi and Battifora, 1987).

The disease can extend over decades or lead to death within a year. The radiotherapeutic approach in respect to target volume, technique and dose has varied considerably over the years. Radiation therapy while not always curative has proved uniformly useful in promoting tumour regression and pain relief, in locally advanced and metastatic tumour. Pulmonary metastasis is the cause of a large number of deaths but may be asymptomatic, although extensive, for many years. Most failures of treatment occur at primary tumour sites or at the site of distant metastasis, whereas failure in regional lymph nodes was uncommon. The usual cause of recurrence is tumour remaining at the surgical margins with no post-operative radiotherapy follow-up (Karen *et al.*, 1977).

Belson *et al.* (1982) report a female prevalence of ACC and the rates of subsequent occurrence of breast cancer suggests an association between these two malignancies. Molteni *et al.* (1981) assessed various head and neck tissues

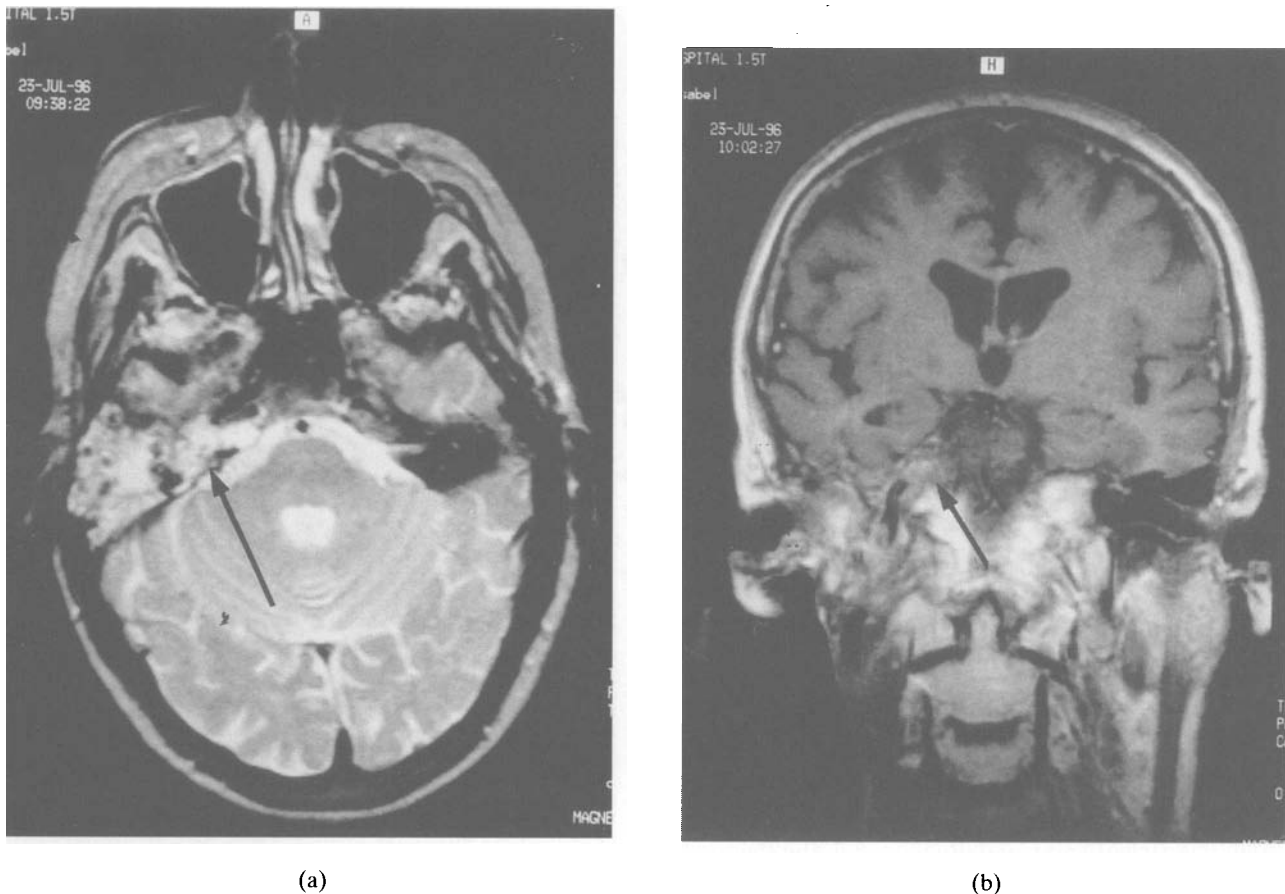


FIG. 2a, b

MRI scans demonstrating the improvement with tamoxifen.

for ER and concluded that both normal and neoplastic salivary gland tissue may be hormone dependent. In another study, by Lamey *et al.* (1987) in which eight patients with salivary tumours were studied, the absence of hormone receptors in these glands suggested that pleomorphic, mucoepidermoid and adenocarcinoma were not dependent on endocrine function.

The management of ACC is that of a disease with an unpredictable pattern. The philosophy of management consists of a variety of surgical procedures and irradiation. Chemotherapy has not been reported to be effective. Cure rates are low and morbidity may be drawn out over 10–20 years. It was 16 years in our patient.

In a review of 100 cases, post-operative radiotherapy improved the local control rates of ACC with advanced local disease, its effectiveness related directly to the extent of the tumour present. Radiotherapy was effective for microscopic disease and 14 per cent suffered local recurrence after radiotherapy, whereas 54 per cent recurred without radiation treatment (Karen *et al.*, 1977). Clearly the ineffectiveness of surgery and radiotherapy to achieve the desired success leaves tamoxifen as a feasible addition at any time in the treatment of ACC. It certainly did arrest the spread of intracranial disease in our patient who was symptomless for almost two years.

Tamoxifen is an oestrogen receptor antagonist used in the treatment of breast cancer. It is used for: (1) initial therapy in women with advanced breast cancer at presentation, (2) patients with metastatic disease; and (3) as adjuvant therapy for early breast cancer in both pre- and post-menopausal women.

Over 30 per cent of patients with metastatic breast cancer respond to tamoxifen. The figure rises to 60 per

cent in oestrogen receptor-positive tumours; for receptor-negative tumours, response rates fall to less than 10 per cent (BNF, 1994). The recommended dose is 20 mg daily. The side effects of tamoxifen include exacerbation of menopausal symptoms in post-menopausal women and amenorrhoea in pre-menopausal women.

The effectiveness of hormone therapy in breast and prostatic cancer is well established. Steroid hormone receptors have been identified in melanomas and squamous cell carcinoma, carcinoids and meningiomas (Kolar *et al.*, 1994). The identification of oestrogen receptors (ER) in bundles of smooth muscle suggest that oestrogens may physically modulate cellular activity. The polypeptides expressed by hormone-dependent tissue after an oestrogen stimulus are designated oestrogen inducible proteins (EIP). These could serve as tumour markers of prognostic significance (Kolar *et al.*, 1994). Salivary gland tumours expressed a strong positivity to steroid receptors and EIP in the same study.

Further immunohistochemical studies of the ER and tamoxifen may certainly be able to pave a new path for the treatment of ACC. It has been shown or inferred that salivary gland may be hormone dependent and oestrogen metabolism may occur there (Dimey *et al.*, 1987). Anti-oestrogen therapy alone or combined with chemotherapy in selected individuals with local-regional recurrence or metastasis is a novel approach in this disease.

Our patient demonstrated some of the clinico-pathologic features of adenoid cystic carcinoma discussed above, that is, regional metastases, direct invasion and recurrence when post-operative radiotherapy was not administered. The response to tamoxifen was definitely encouraging.

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