

Photodynamic-therapy-activated immune response against distant untreated tumours in recurrent angiosarcoma

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We report the case of a 64-year-old Chinese man with histologically proven multifocal angiosarcoma of the head and neck. To our knowledge, this was the first clinical case in which regression of untreated distant tumours was noted after photodynamic therapy. The patient was treated initially with high dose rate brachytherapy by use of an iridium-192 (¹⁹²Ir) source for a total dose of 36 Gy over six fractions. The tumours showed regression, but recurred within 1 year. Further treatment options, including radiotherapy, surgery and photodynamic therapy, were discussed. The patient subsequently consented to photodynamic therapy, which was carried out in an outpatient clinic. We used a new generation photosensitiser, Fotolon (Haemato-science GmbH, Luckenwalde, Germany), which comprises

chlorin e6 and polyvinylpyrrolidone (molecular weight 12000) in the ratio of 1:1. Unlike first generation photosensitisers, which rendered patients light sensitive for up to a few weeks, Fotolon clears rapidly from the body within 24 h.¹ Fotolon was prepared freshly by dissolving 0.2 g of Fotolon in 100 mL of 0.9% saline. The preparation was administered intravenously at a dose of 2.0–5.7 mg/kg body weight over 10–20 min. 3 h later, the tumours were irradiated with laser light of wavelength 665 nm (\pm 3 nm) for a total light dose of 65–200 J/cm², delivered at a fluence rate of 80–150 mW/cm². The table shows the treatment parameters used during each administration.

We did not note any side-effects or complications during or after treatment, other than transient pain at the

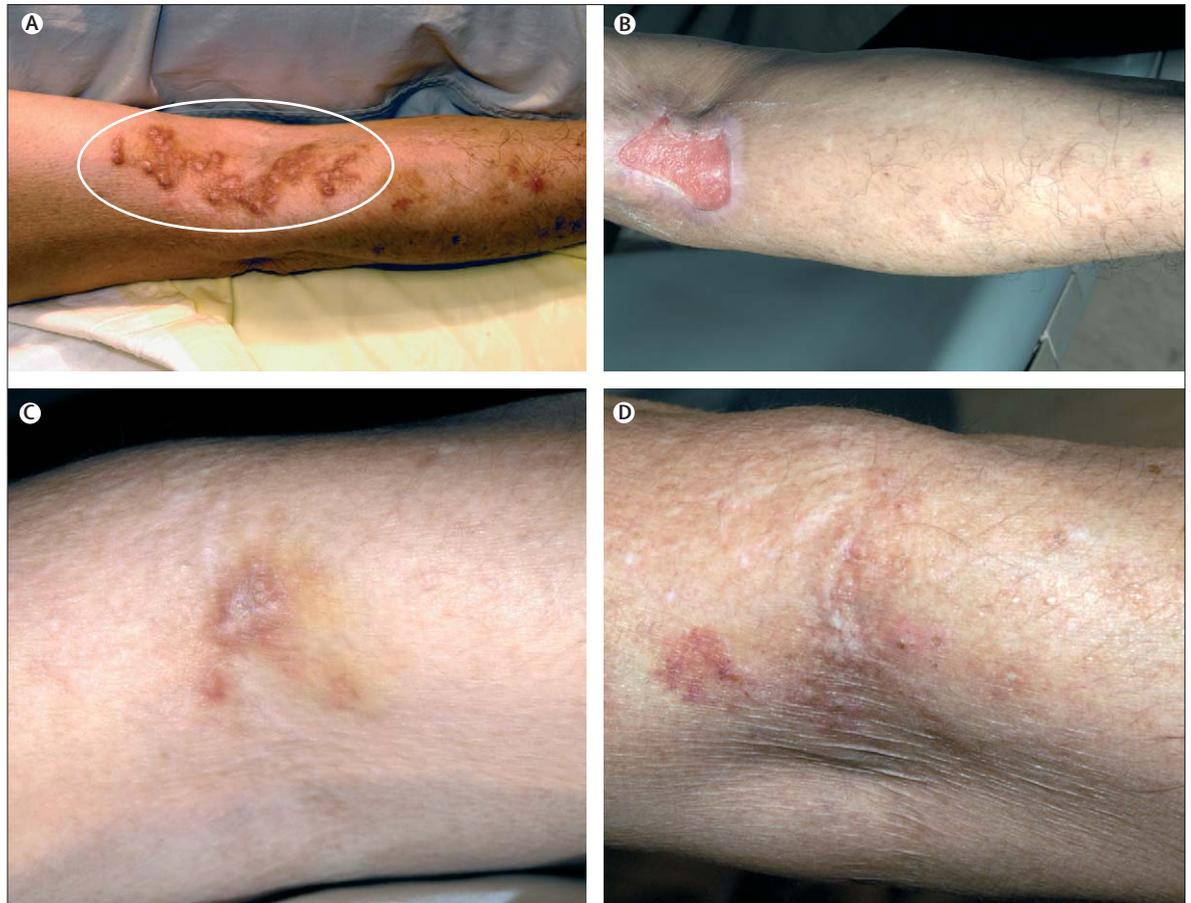


Figure 1: Angiosarcoma on upper limbs

(A) Main cluster (circled) before photodynamic therapy on right upper limb. (B) Scarring at site treated with photodynamic therapy and spontaneous regression of untreated tumours on right upper limb 2 months after treatment. (C) Tumours on left upper limb before photodynamic therapy. (D) Spontaneous regression of untreated tumours on left upper limb 4 months after photodynamic therapy.

	Tumour site	Fotolon dose (mg/kg)	Injection volume (mL)	Light fluence rate (mW/cm ²)	Light dose (J/cm ²)
First photodynamic therapy	Right forehead	5.7	200	150	200
	Nasal bridge	5.7	200	100–150	200
1 week later	Left occiput	5.7	200	150	200
	Right occiput	5.7	200	150	200
	Nape	5.7	200	150	200
10 months later	Right lower arm	4.0	140	82	100
	Right upper arm	4.0	140	82	200
21 months later	Right occiput	2.0	70	80	65

Table: Photodynamic therapy and timeline

treatment site. Photodynamic therapy was effective in achieving local control of the tumours for 14 months; this treatment was assessed by macroscopic measurement of the tumour sizes. 10 months after treatment, new tumours were noted in both upper limbs (figure 1). Photodynamic therapy was administered to the main cluster of tumours on the right upper limb. The untreated tumours on the same limb underwent spontaneous remission 2 months later; likewise, the untreated tumours on the other limb underwent spontaneous remission 4 months after treatment (figure 1). Sustained remission of these tumours was achieved for 15 months after treatment. Remission was assessed by the clinical observation. 14 months after the initial treatment, recurrences of angiosarcoma at the previous sites on the head and neck were noted. At this time, the patient initially refused photodynamic therapy due to pain at the treatment site; but photodynamic therapy was repeated at 21 months on the right occiput only at decreased drug and light doses (table). Biopsy of the untreated left occiput tumour at 48 h showed a moderately dense perilesional T lymphocyte infiltrate. CD4+ T lymphocytes comprised 95% of the infiltrate, and CD8+ cells formed the remainder (figure 2). However, repeat biopsy of the same

site 1 month later showed a predominantly CD8+, CD4- T-lymphocytic infiltrate (figure 2). Subsequently, further biopsies of these tumours did not suggest malignancy.

Angiosarcomas are rare, malignant vascular tumours. Although they can occur anywhere in the body, 60% occur in skin or superficial soft tissue, of which half occur in the head and neck region, especially on the scalps of elderly men.² The conventional treatment for this malignancy include radical surgery, chemotherapy, radiotherapy, or a combination of these options. Due to multifocality and diffuse, clinically unapparent spread, complete resection is often difficult. Generally, however, angiosarcomas are high-grade aggressive tumours that tend to recur locally and metastasise early, despite multimodality treatment. The overall prognosis is poor and the reported 5-year survival is 10–35%.^{2,3} New immunotherapeutic approaches have been reported. Recombinant interleukin-2 with radiotherapy has been shown to be effective for the treatment of angiosarcoma of the scalp.⁴ Furthermore, case reports have been published on effective local control with the use of interferon and chemotherapy or radiotherapy.^{5,6}

Photodynamic therapy is a new modality in cancer treatment, and uses a photosensitising drug that

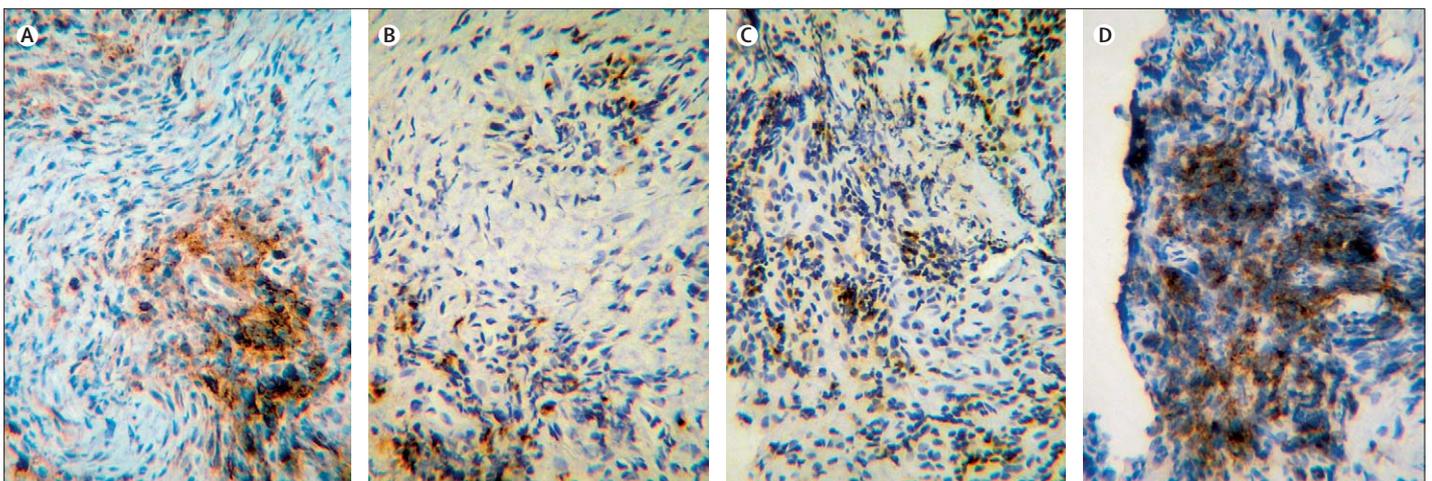


Figure 2: Biopsy from left occiput

48 h after photodynamic therapy showed (A) heavy CD4+ T-cell infiltrate, and (B) few CD8+ T cells (magnification x100). (C) Repeat biopsy of same site 1 month after photodynamic therapy was negative for CD4+ T cells (magnification x100), and (D) stained strongly for CD8+ T cells (magnification x200).

accumulates preferentially in tumours. Subsequent irradiation of the tumour with light of an appropriate wavelength generates reactive oxygen species, with singlet oxygen as the predominant cytotoxic component, leading to tumour death. In addition to direct killing of cancer cells, the mode of action of photodynamic therapy includes vascular damage, which leads to tumour infarction, and activation of an immune response against tumour cells. A combination of these three mechanisms of tumour eradication by photodynamic therapy is thought to contribute to long-term tumour control.^{7,8} In this report, we present photodynamic therapy as a viable option for the treatment of recurrent angiosarcoma.

Other studies have shown the importance of immunity induced by photodynamic therapy in the treatment of cancers, and have suggested that cell-mediated responses have an important role; this immune response resembles inflammation, with macrophages and dendritic cells acting as antigen-presenting cells. Presentation of tumour-specific peptides lead to the recognition of tumour antigens by CD4+ helper T lymphocytes, which then sensitise CD8+ cytotoxic T lymphocytes. Animal studies have shown that generation of tumour-targeting CD4+ and CD8+ T-cell clones lead to tumour immunity, not only at sites that have undergone photodynamic therapy, but also distant metastatic tumours.^{7,8} A study in human beings showed that patients with vulval intraepithelial neoplasia (VIN) who do not respond to topical photodynamic therapy with the use of 5-aminolevulinic acid were more likely to show HLA class I loss compared with responders.⁹ The study also showed a significant increase in CD8+ T-lymphocytic infiltration in VIN responders after treatment compared with non-responders.⁹

We have previously shown that photodynamic therapy induces apoptosis and necrosis of tumour cells.^{10,11} The balance between apoptosis and necrosis depends on parameters such as drug and light doses, light-fluence rate, drug-light interval, and intracellular localisation of the photosensitiser.^{8,11} We postulate that after photodynamic therapy with Fotolon, immunogenic peptides are generated from tumour cells that are undergoing apoptosis or necrosis, or both. Presentation of these peptides by antigen-presenting cells could lead to the activation and proliferation of peptide-specific cytotoxic CD8+ T-cell clones. This process is supported by the shift from a CD4+ to a CD8+ T-cell infiltrate in the tumour in our patient. Although we have not established whether

these tumours were due to field cancerisation or metastasis, the response we noted was specific. Therefore, we postulate that a common antigen might have been expressed for all the tumours in our patient. We believe that this tumour-specific cell-mediated response led to the remission of neighbouring and distant untreated tumours in the upper limbs after photodynamic therapy of selected new tumours on the right upper limb.

In summary, photodynamic therapy is a viable treatment option for local control of recurrent or inoperable angiosarcoma. Furthermore, this treatment can be administered repeatedly without development of resistance or major adverse effects. We hypothesise that, in addition to its better-known effects on tumour vasculature, photodynamic therapy causes regression of tumours by cell-mediated immunity. Photodynamic therapy might become an important treatment option in patients with multifocal, immunogenic tumours.

Conflicts of interest

The authors declared no conflicts of interest.

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