

Visceral metastatic angiosarcoma treated effectively with oral cyclophosphamide combined with propranolol



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INTRODUCTION

Angiosarcoma is rare soft tissue sarcoma of endothelial cell origin occurring mainly in white elderly people.¹ The most common clinical location is the head and neck. Only a few chemotherapeutic drugs are available for the therapy of metastatic angiosarcoma, with poor results and bad tolerance: paclitaxel or doxorubicin (with a progression-free survival of 3.7 to 5.4 months for nonresectable angiosarcomas treated with doxorubicin²). Cyclophosphamide is safe and easy to use in elderly patients with metastatic angiosarcoma but is of low efficacy used alone. Cyclophosphamide has both an antiangiogenic and an immunomodulating effect.

β -blockers show a remarkable efficacy in the treatment of benign vascular tumors such as infantile hemangiomas.³ Hemangioendotheliomas and angiosarcomas are reported to express high levels of β adrenergic receptors.⁴ This finding suggests that effectiveness of β -blockers may be extended to aggressive vascular tumors. Propranolol is a nonselective β -adrenoceptor antagonist, which inhibits angiogenesis and induces apoptosis.^{4,5} Recently, a few studies reported an efficacy of β -blockers in the treatment of angiosarcoma.^{4,6-8}

CASE REPORT

We report the case of a 73-year-old white man who had a relapsing angiosarcoma of the scalp since 2009 and underwent multiple surgeries. The last one was performed in 2014. The patient's medical history included obesity, arterial hypertension, and type 2 diabetes complicated with renal failure. In October

Abbreviations used:

CR: complete remission
PR: partial remission

2015, he presented with mediastinal, hepatic, adrenal, and cutaneous metastases. Cutaneous and mediastinal metastases were confirmed by histology (Fig 1, A and B). The patient was treated, after his consent, with metronomic oral cyclophosphamide (Endoxan) at a dose of 100 mg twice daily, 1 week out of 2, along with β -blocker, and propranolol, 120 mg daily divided into 2 doses of 80 mg and 40 mg. After 3 months of treatment, the patient experienced a partial remission (PR) according to Response Evaluation Criteria In Solid Tumors,⁹ with a response rate of 27% for visceral metastasis, and a complete remission (CR) for cutaneous metastasis. At the following tumor assessment 5 months later, the PR was maintained (response rate of 31% in visceral metastases) and CR confirmed for cutaneous lesion. At the last evaluation available after 7 months, the PR was confirmed, with a regression of 44% for visceral metastasis and no relapse of cutaneous lesions (Fig 2, A and B). The safety was good with only a grade 1 anemia (Common Terminology Criteria for Adverse Events). The treatment is still ongoing.

DISCUSSION

We report a rare case of visceral metastatic angiosarcoma effectively treated with propranolol combined with oral cyclophosphamide with a PR after 7 months of follow-up and good tolerance

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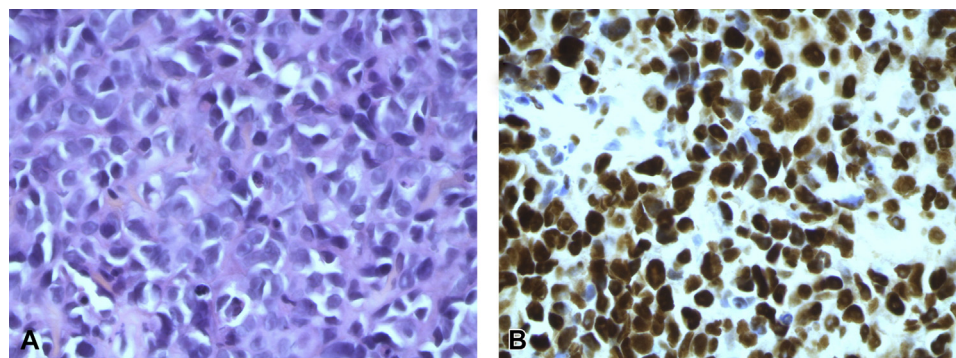


Fig 1. Histologic image of subcutaneous scalp metastasis of angiosarcoma. **A**, Epithelioid cells disposed on sheet without angiomatous differentiation on morphologic data. **B**, Intense and diffuse nuclear labelling. (**A**, Hematoxylin-eosin-safran coloration; **B**, Immunomarking ERG; original magnifications: **A** and **B**, $\times 400$.)

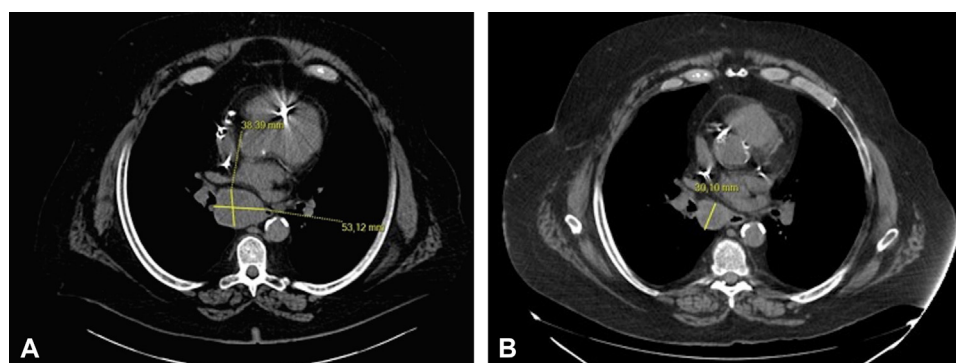


Fig 2. **A**, Mediastinal metastasis at baseline. **B**, Mediastinal metastasis after 7 months of treatment: PR.

associated with an excellent quality of life. Chemotherapy was not attempted first because the patient was elderly with comorbidities, and traditional chemotherapy involves significant toxicities.

To our knowledge, only 9 cases were previously reported^{6,8,10} in the literature (8 metastatic angiosarcomas, 1 cutaneous multifocal angiosarcoma). Seven patients received propranolol combined with chemotherapy (vinblastine and methotrexate or paclitaxel) followed by maintenance treatment with propranolol, etoposide, and cyclophosphamide, with 1 CR and 6 PR and a median progression-free survival of 11 months. One patient received propranolol, paclitaxel, and radiotherapy. Only 1 patient received the combination of propranolol and metronomic oral cyclophosphamide, as with our patient, but with lower doses (propranolol, 40 mg/d, and cyclophosphamide, 50 mg/d). A CR was obtained for 20 months. As in our case, no severe toxicity was noted. Unlike previously published cases, we did not use induction treatment with intravenous chemotherapy followed by maintenance treatment. Our therapeutic approach uses

higher doses based on the high-level expression of β adrenergic receptors in angiosarcoma described in the literature.⁴

CONCLUSION

This clinical case suggests that the combination of propranolol and cyclophosphamide could be a pertinent alternative to chemotherapy in angiosarcoma with a good tolerance in the elderly. Finally, an increasing number of case reports with objective tumor responses call for a clinical trial studying a combined treatment including propranolol and classical chemotherapy in cutaneous angiosarcoma.

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