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Pulmonary Epithelioid Hemangioendothelioma: Advances in Treatment Options despite a Rare Vascular Tumor

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Introduction

We have already discussed about dail and liebow describing pulmonary epithelioid hemangioendothelioma (PEH) as an aggressive bronchoalveolar cell carcinoma with a remarkable propensity to invade adjacent blood vessels and small airways, the following Weiss and Enzinger description of epithelioid hemangioendothelioma (EHE) as a vascular bone and soft tissues tumor showing intermediate malignancy between hemangioma and angiosarcoma, and the final confirmation from Weldon-Linne of a factor-VIII-related antigen onto malignant cells [1]. The recent World Health Organization (WHO 2002) classification has described EHE as lesions that fall into the category of locally aggressive tumors with metastatic potential [2,3]. The etiology of EHE is still a dilemma, as several clonal abnormalities in tumor cells, and different angiogenic stimulators may act as promoters of endothelial cell proliferation [4-8]. A new etiopathogenetic hypothesis suggests a causal relationship between chronic Bartonella infection and the development of this rare vascular tumor: if this was confirmed, it would be plausible that eradicating the bacterial infection or interrupting Bartonella-induced angiogenic and proliferative cell signals could slow the tumor progression and improve patient outcomes [9].

Due to its rarity (EHE represents less than 1% of all vascular tumors), because of EHE clinical presentation is as heterogeneous as its clinical localization can be, there is no standard for treatment and few therapeutic options are available. As the most common presentations are liver alone (21%), liver plus lung (18%), lung alone (12%) and bone alone (14%), the available literature focuses above all on these three directions [10]. The general issue seems to be that, when bone or pulmonary lesions are small and limited in number, surgical, curative resection (that is amputation, en-bloc resection, wedge resection) achieves good outcomes [11,12]. Locally advanced hepatic EHE seems to benefit from transplantation, with good results [13]. However, a complete surgical resection is not usually feasible: Pinet et al. reported a case of an aggressive form of pleural EHE resulting in complete remission after treatment with carboplatin plus etoposide [14], as well as bilateral multicentric PEH seems to respond well to interferon 2α, with some partial spontaneous regression [7]. Nonetheless, when a pathological fracture occurs, a great alternative to plate-and-screws surgical stabilization is radiofrequency ablation: by creating small, carefully controlled, thermal injuries of bone, the extent of resection can be reduced [15]. On the other side, with the aim of controlling residual desease given the recurrence of EHE, radiation therapy (RT) is chosen for localized EHE, while chemotherapy is preferred for widespread disease. In any case, the beneficial effect of both is still not confirmed [14,16-19]. Given the vascular origin of this tumor, the use of antiangiogenetic molecules like thalidomide and lenalidomide reasonably might achieve good outcomes (partial response and several stable diseases), even if using bevacizumab and nanoparticle albumin-bound paclitaxel (nab-paclitaxel) produced higher percentages of progression disease [20]. RT has proven to be ineffective for PEH because of the tumor's radiobiological characteristics (slow growth of the tumor cells), while a good local control has been obtained in EHE of bone [19, 21] Since EHE has been correctly defined, several research groups have dealt with EHE bone irradiation, in order to define the volume and the dose distribution achieving the greatest results for local disease control, together with the greatest tolerance to the treatment and the lowest incidence of side effects [19,21-24]. A 6400 cGy adjuvant RT was also performed against an axillary form of EHE, resulting in the absence of lymph nodes metastases but pleural and pulmonary widespread [18]. In our experience, at our Institute we observed systemic progression of EHE after 4-month-PEG-IFN-α therapy in spite of stable pulmonary disease; then, lumbar pain control with good tolerance and better quality of life at 1-year-follow-up from a symptomatic, normofractionated RT onto the L3-L5 vertebral tract, consolidated outcome through Ifosfamide and Epirubicin chemotherapy soon after RT, and surgical removal of EHE spleen lesions, showing 1-year survival [1].

All this considered, despite the rarity of this vascular tumor and its extremely complex and heterogeneous patterns of presentation, actually we are capable of performing more treatment lines, combined in a multimodal strategy or sequencially adopted, so that we are able to reach good outcomes in most of cases. In this regard, taking into account the EHE radiobiological characteristics, no doubt evidence is all in favour of RT obtaining local pain control with good tolerance and better quality of life at least one-year-follow up. The literature reveals certain discordance about the radiation dose to be used for this purpose, maybe attributable to the very small number of patients and to the limited survival that EHE typically shows. As a result, further studies are needed to answer the question.

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