

Radiotherapy as an Effective Primary Treatment for Epithelioid Haemangioendothelioma of the Cervical Spine

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Abstract. *Epithelioid haemangioendothelioma (EHE), first described in 1982, is an uncommon malignancy comprising of around 1% of all vascular tumors and accurate diagnosis relies on specialist review of histology. Cervical spinal primaries are very rare and standard treatment for localized disease is surgery. Data regarding management of localized but unresectable tumors are limited. We undertook a literature review in order to highlight its clinico-pathological features and we describe a first case of an unresectable cervical EHE, successfully treated with radical radiotherapy.*

Case Report

We describe the case of a 55-year-old man who presented himself to the emergency department in 2002 with severe neck pain. His symptoms had started three weeks prior to presentation and initial X-ray of his cervical spine showed an infiltrative lesion from C2 to C4 (Figure 1). On clinical examination, localized pain was documented but systemic examination was unremarkable with no neurological signs found. A collar was applied and the patient was prescribed codeine phosphate for his pain. Cervical MRI revealed the lesion to be constricting the cord at the affected level with posterior extension into the pars interarticularis on the left. The tumour measured a maximum cranial-caudal distance of 4 cm and staging ultrasound of the neck and CT scan of the chest, abdomen and pelvis did not reveal metastases.

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The patient was referred for a CT-guided biopsy of the lesion and tissue was reviewed by a pathologist from a national specialist Orthopaedic Unit. Formal histological report described the lesion as consisting of cords and nests of epithelioid cells, some of which had intracytoplasmic vacuoles embedded in a myxo-hyaline stroma. There was no evidence of angiosarcoma and cells showed immunopositivity to CD31. Pathological features were confirmed to be that of EHE (Figure 2).

The patient's case was discussed in the sarcoma multidisciplinary meeting and in view of the proximity of major vessels apposed to the tumour, it was considered radically unresectable. Referral was then made to the clinical oncology team for consideration of radiotherapy. The patient was CT-planned for radical radiotherapy and the tumour was treated to a dose of 55 Gy in 32 fractions over 43 days using 6 MV photons with a 3-field plan. The patient tolerated treatment well, without any severe side effects. At clinical review four months after treatment, his pain had resolved and it was possible to remove his collar. The patient was followed-up annually and has ever since remained in remission with no signs of relapse.

Background. EHE was first described by Weiss and Enzinger in 1982 (1). It is a rare tumour of endothelial origin, accounting for 1% of all vascular neoplasms (2). It has been described to occur in visceral organs (lungs, liver, spleen and heart) as well as in bones. Skeletal EHE are more common in peripheral bones, mainly affecting the lower extremities but only 10% present in the vertebral column (3).

Spinal EHEs are uncommon and where lesions occur, they do so mainly in the thoracic and lumbar vertebrae. The first case of lumbar involvement was reported by Ellis *et al.* (4) in 1996. The longest follow-up of eleven years was described by Aquilina *et al.* (5) in a seventeen-year-old patient with T10 involvement, who received vertebrectomy and post-operative radiotherapy. In a case series of eight patients with spinal EHE by Aflatoon *et al.* (3), three occurred in the thoracic



Figure 1. Lateral cervical spine X-ray showing the lesion at C2-4.

spine and five were lumbar primaries. Tumours may occur as a solitary lesion, multi-centric or with metastases. Cervical primaries are very rare.

EHE is common in caucasians (1) and differences in frequency of incidence between males and females have not been consistently observed (3, 6-8) Age of presentation may range from five to seventy-four years (3, 5, 9), peaking in the second and third decades (6, 8, 10) with the median age of presentation reported at twenty-seven years (3). The tumour is classically described as of low (3) to intermediate malignancy between that of haemangiomas and angiosarcomas, while both indolent and aggressive diseases have been identified. There has been no consistent correlation between histological grade, multi-centricity, site and radiological appearance with clinical outcome (2, 6, 7). Local recurrence rate is around 10 to 15%, and 20 to 30% of cases develop metastases. Mortality attributed to EHE ranges from 10 to 20%, but is higher for bony tumours with synchronous parenchymal disease (7, 11).

Histological features. EHE are composed of ribbons or nests of rounded and slightly spindled endothelial cells. The cells have ample cytoplasm and may contain intracytoplasmic vacuoles. Minimal nuclear atypia, mitotic activity or pleomorphism is usually found. Stroma may range from

being hyaline to myxoid, but rarely chondroid or sclerotic in appearance. These tumours may show a spectrum of changes ranging from well-formed vascular channels lined by atypical endothelial cells to high-grade forms which exhibit nuclear pleomorphisms, necrosis and mitotic activity resembling angiosarcoma. Tumours may stain positive for Factor VIII- related antigen (6) and endothelial markers CD31 and CD34. Focal keratin expression is not uncommon. Although high-grade tumours have been suggested to have a negative impact on prognosis (6), this has not been confirmed in a review of published case series (3, 7).

Clinical features. Clinically, pain is the most common presented feature. Duration of symptoms prior to presentation ranges from several weeks to two- (3) and even ten (6) -years in retrospective studies. Localised tenderness or swelling may also be present, with or without fracture (10). Neurological compromise, included paraspinal spasms, paresthesia, radiculopathy and frank paraplegia. Local bleeding and development of haematoma has been also reported (9).

Radiological features. On imaging, the lesions appear as an enlarging mass, often less than 5 cm in length for solitary cases. It is commonly described as expansile and osteolytic, with a “soap bubble matrix” appearance. Tumour edge may look distinct or diffuse with frequent local bone destruction. Most authors do not describe periosteal reaction (3, 7) but its presence has been associated with high-grade lesions (6, 12). Local CT scanning is useful in assessing the degree of bone destruction and spinal stability when considering surgery. Furthermore, non-enhancement with contrast suggests EHE as opposed to haemangiomas (2). On MRI, vascular bone tumours show higher signals compared with skeletal muscle but lower than fat on pulsed T1-weighting. This feature becomes more emphasised on pulsed T2 (2). Nevertheless, imaging-alone has a low-diagnostic sensitivity and tumour biopsy should always be advocated. Available tissue should be reviewed by a specialist histopathologist to arrive at a diagnosis of EHE.

Treatment for localised spinal EHE. Surgery is the standard curative option for localised tumours followed by spinal stabilisation, if necessary. Haemorrhage is a frequent complication and pre-operative angiography may aid surgical planning, with the possible option of tumour embolisation to help stem intra-operative blood loss.

The risk of local recurrence after primary surgery is around 13% (1). Adjuvant radiotherapy to a dose of 55 Gy has been reported to be effective in maintaining local control up to twenty-six months in a patient with resected thoracic EHE (2). For patients without spinal instability, radiotherapy may also be used as primary treatment. Literature suggests

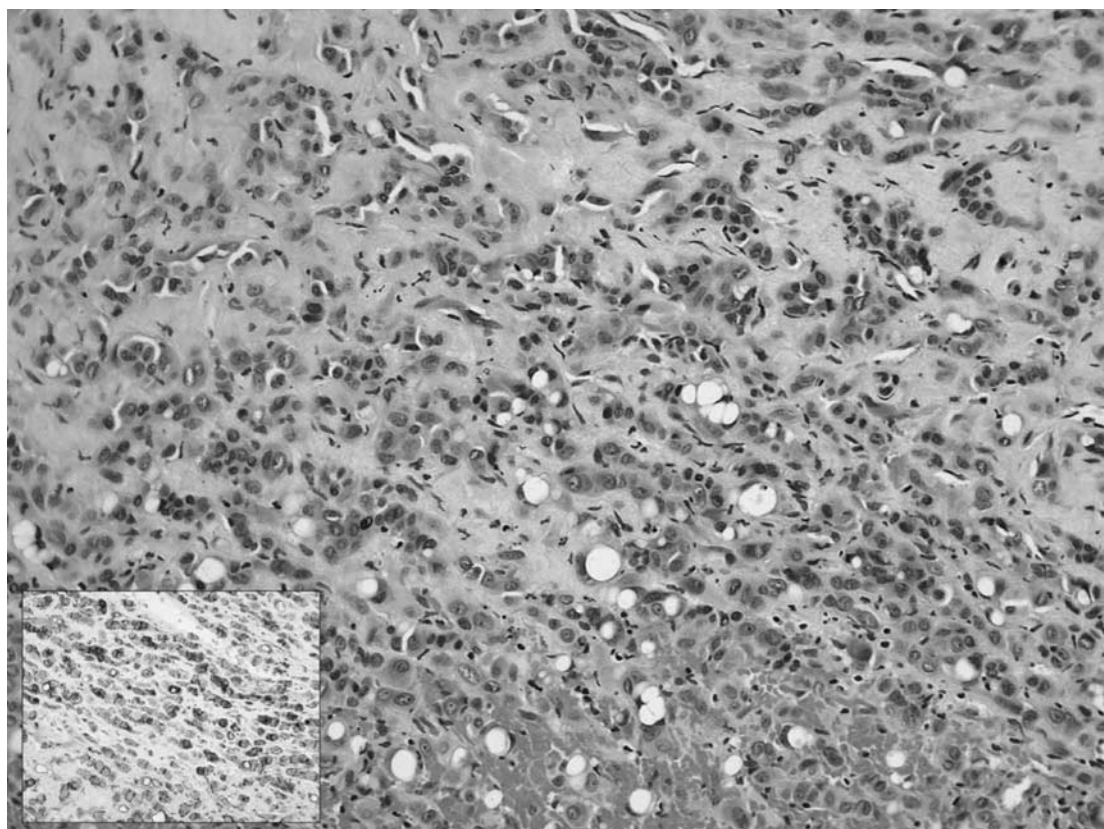


Figure 2. Histopathology slide from tumour biopsy showing EHE consisting of clusters and cords of cells set in a myxo-hyaline matrix. Some cells have intracytoplasmic vacuoles. Inset: CD31 stains neoplastic cells.

EHE to be a reasonably sensitive tumour showing response to a dose of 30-40 Gy (13). However, secondary malignancy, especially sarcoma, is a recognised complication with an estimated incidence of $\leq 1\%$ after 4000-7000 rads (14).

A case series by Aflatoon *et al.* (3) consisted of eight patients with thoracic or lumbar spinal EHEs. Seven had surgery involving tumour curettage or laminectomy. Out of the five who received post-operative radiotherapy, one developed secondary sarcoma after a radiotherapy dose of 4000 rads at four years. One patient who received radiotherapy-alone eventually progressed with lung metastases.

In a study by Kleer *et al.* (7) which included seven spinal primaries, twenty-six cases out of the overall forty were followed-up for an average of 4.3 years (2 months to 11 years). Although some patients were treated with surgery-alone, others received post-operative radiotherapy or chemotherapy. One out of two patients who had adjuvant radiotherapy after curettage was free of local recurrence, compared to primary curettage-alone. Ten patients received radiotherapy, but it was unclear from the report regarding the indication, site or dose of treatment as half of these patients had visceral metastases at presentation.

Tsuneyoshi *et al.* (8) presented fourteen cases of EHE of the bone, two of which were of spinal origin. One patient achieved four-year local disease control after tumour curettage-alone and the other was in remission at twenty-month follow-up after local resection followed by adjuvant radiotherapy.

Wold *et al.* (6) reported on 112 patients with bony haemangioendothelial sarcoma of the bone. Although this large series included patients with pathological diagnoses prior to the publication by Weiss, it included thirty-eight patients who were treated with radiotherapy. Twenty-one patients had radiotherapy-alone, eight after surgery, seven with chemotherapy but without surgery and two with surgery and chemotherapy. 59% (22/38) had tumours which were inaccessible to surgery. 13/27 (48%) achieved local control after radiotherapy without development of metastases. Successful treatment was related to radiotherapy dose, where 93% of those receiving ≥ 5000 rads compared to 55% of those receiving < 5000 rads, achieved local control. Likewise 75% of those receiving the higher-dose survived compared to 40% in the lower-dose after a mean follow-up period of 2.9 years (one month to nineteen years). Unfortunately, stratification of

data according to primary *versus* adjuvant radiotherapy and peripheral *versus* axial primaries, were not available.

Conclusion

Due to the rarity of spinal EHE, no randomised data are available and management of individual patients rely on analysis of individual case reports and cohort series. The challenge remains to offer patients with effective treatment options in surgically-inaccessible tumours. Even though there has not been any direct comparison between curative surgery and radical radiotherapy, available evidence suggests EHE could respond to high-dose radiation treatment-alone. Although adjuvant radiotherapy is commonly used to reduce the risk of local recurrence, its potential role as primary treatment remains to be explored. In cases where radical resection is not possible, radical radiotherapy should be considered.

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