Extraosseous Ewing Sarcoma of the Larynx: A Report of a Rare Case

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Abstract

Objectives: Extraosseous Ewing sarcoma is a variant of Ewing sarcoma that can occur anywhere in the body. There are few documented cases reported in the head and neck region and only two reported cases arising from the larynx.

Methods/Results: We report a case of a 45-year-old female who was found to have primary extraosseous Ewing sarcoma of the larynx. Initial workup of her new neck mass, appearing to arise from the thyroid gland, was concerning for lymphoma based on fine needle aspiration. However, further biopsy and immunohistochemistry confirmed a much different diagnosis. She received the current recommended therapy for this rare disease that has a high rate of recurrence.

Conclusions: These tumors can be mistaken for other neoplasms due to their primitive morphology and rare occurrence. We discuss the workup to allow for accurate diagnosis, treatment, and prognosis to improve morbidity and mortality from this rare disease.

Introduction

Ewing sarcoma (ES) is a rare, high-grade, malignant neoplasm composed of small round blue cells that originate from mesenchymal stem cells and commonly present in the skeletal system. ES is the second most common bone cancer, typically presenting in children, adolescents, and young adults.[1-3] Rarely, it can arise in extraosseous sites, such as the lung, skin, pelvic cavity, retroperitoneum, and the head and neck region.[4,5] Extraosseous Ewing sarcoma (EES) accounts for 1.1% of malignant soft tissue tumors with 9% of them localized to the head and neck. Of these, 1-4% are diagnosed in otolaryngeal areas.[4,6] The unusual site of involvement combined with the primitive morphology of EES can make diagnostic accuracy challenging, as it often mimics other neoplasms.[4,7]

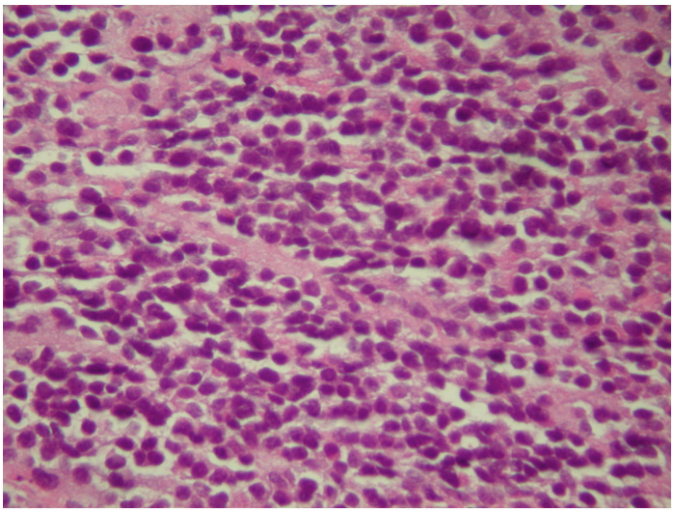
To our knowledge, there have been only two previously reported cases of EES involving the larynx.[3] We report a rare case of a 45-year-old female diagnosed with primary EES arising from the right larynx, initially thought to be lymphoma on outpatient evaluation of her neck mass. The diagnosis, pathogenesis, treatment, and literature review is discussed below.

Case Report

A 45-year-old white female presented for routine follow-up for breast cancer to her oncologist. She developed a new anterior neck mass that gradually increased in size over a one-month period. The mass seemed to arise from her thyroid gland and was associated with hoarseness. The remainder of her clinical history was unremarkable. Her past medical history is significant for invasive ductal breast carcinoma which was diagnosed three years prior. She underwent a modified radical mastectomy and completed a course of adjuvant chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel. This was followed by adjuvant tamoxifen planned for five years. Physical examination of her neck revealed smooth, rubbery, non-tender masses bilaterally without palpable lymphadenopathy. Nasopharyngolaryngoscopy demonstrated complete unilateral right vocal cord paralysis with associated edema.

A thyroid ultrasound showed a 2.9-cm complex, hypoechoic mass in the right upper pole of the thyroid, a separate 1.9-cm nodule anterior to this, and a 7 mm nodule in the left lower pole. All three nodules appeared to arise from thyroid tissue. Ultrasound-guided fine-needle aspiration of the right dominant nodule revealed atypical lymphoid elements suspicious for lymphoma. A subsequent positron emission tomography/computed tomography (PET/CT) was then obtained revealing two masses adjacent to, but distinct from, the thyroid gland, both of which were intensely fluorodeoxyglucose (FDG) avid. There were no sites of metastatic disease identified.

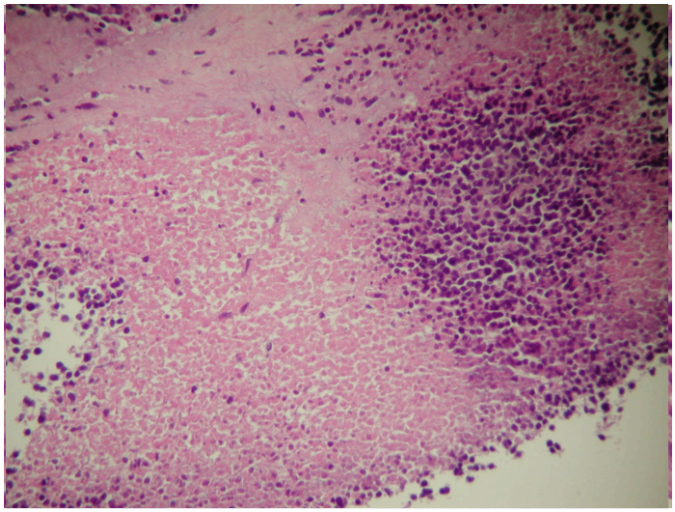
Figure 1: Hematoxylin and eosin stain of cell block showing small round blue cell tumor with scant cytoplasm



Additional tissue sampling was recommended to confirm the diagnosis of lymphoma; therefore, an excisional biopsy of the right thyroid mass was performed. Final pathology was consistent with EES. Neoplastic cells were positive for cluster of differentiation 99 (CD99), FL1-1 and weakly positive for synaptophysin. Fluorescence in situ hybridization (FISH) was positive for t(11;22). Sections demonstrated diffuse proliferation of small round blue cells with scant cytoplasm, inconspicuous nucleoli, and necrosis (Figure 1, Figure 2). Flow cytometry was negative for lymphoma and thyroid tissue.

The patient was referred to a tertiary care facility for further treatment. Within one month of her biopsy, the neck lesions had grown significantly with worsening hoarseness. She then underwent pan endoscopy and biopsy of a lesion that clearly emanated from the right larynx. This biopsy was also consistent with EES. She immediately began treatment with four alternating cycles of modified vincristine, doxorubicin, and cyclophosphamide (VDC) with alternating ifosfamide and etoposide (IE) given over four days instead of the usual two to avoid cardiotoxicity given her prior doxorubicin exposure. She went on to receive two cycles of concurrent radiation as well as two additional cycles of IE. Near resolution of her hoarseness was achieved with induction of chemotherapy. Three months after her final radiation treatment, follow-up PET/CT showed significant volumetric and metabolic improvement in the perilaryngeal soft tissues when compared to prior PET/CT; however, there was a new FDG avid spot on the sacrum (S1). Repeat nasopharyngolaryngoscopy demonstrated resolution of her laryngeal mass. Further MRI evaluation of the pelvis confirmed a 3.3 x 1.6-cm area of marrow replacement as well as cortical breakthrough of S1, concerning for metastatic disease.

Figure 2: Cell block demonstrating tumor necrosis



Discussion

Tefft et al first described EES in 1969 as histologically similar to primary ES of the bone, usually presenting in the lower limbs or paravertebral area.[3,4,6,8] EES is a rare, rapidly growing round cell malignant tumor that can develop in soft tissues at any location. Approximately 80% of ES cases will occur in patients less than 20 years of age, and 80% of these cases will arise from bone, primarily affecting the diaphysis or metaphyseal-diaphyseal regions.[7] In contrast, 50% or more of primary adult cases are extraosseous. For patients diagnosed with EES, approximately 15-46% will present with gross metastatic disease at the time of diagnosis. The most common site of metastasis for EES is the lung, followed by bone which has a particularly poor prognostic factor.[9]

The histological pattern of EES consists of solid sheets of small, round, uniform, primitive cells with round nuclei and scant cytoplasm that lack significant differentiation. These features make EES difficult to distinguish from other tumors such as primitive neuroepithelial tumor, rhabdomyosarcoma, neuroblastoma, small cell carcinoma, and malignant lymphoma.[3,4,7] Immunohistochemical expression of CD99 is helpful in separating this entity from other small round cell tumors; however, it can also be expressed by other sarcomas.[7] Molecular demonstration of the EWS-FL1 gene rearrangement via a FISH study is highly specific for EES and is present in 90-95% of these sarcomas, making this essential for accurate diagnosis. Immunohistochemistry shows positive prostate-specific antigen (PSA), CD99, vimentin, various expressions of neuron-specific enolase (NSE), synaptophysin (SYP), and cluster of differentiation 57 (CD57) and is negative for 100% soluble proteins (S-100) and nuclear factor (NF).[2-7]

Current treatment recommendations by the National Comprehensive Cancer Network (NCCN) for EES are the same as those for bone ES, with the main treatment being chemotherapy, surgery, and radiation.[10] It has been shown that alternating VDC/IE chemotherapy can improve the metastasis-free survival.[4,6,10] Wide resection margins of 2-3 cm in conjunction with multiagent chemotherapy are necessary for good clinical outcomes.[6] Radiotherapy has been regarded as the standard treatment for localized tumor therapy for decades. However, recent data advocates surgery when complete resection is possible.[2] Induction chemotherapy is commonly used due to the high risk of recurrence and metastatic disease and should be given 12-24 weeks before surgery; additional post-operative chemotherapy and radiation is the treatment of choice when possible.[1,4,6] Primary and metastatic ES are unique among sarcomas in that they can respond dramatically to initial therapy.[1,9]

Despite good initial responses to treatment, EES usually follows an aggressive course with a high rate of both local recurrence and distant metastasis.[4,9] Age and surgical treatment were found to be the most important prognostic indicators for response, followed by tumor location, tumor size, presence of metastasis, genetic mutation type, and treatment regimen.[1,6,8] One study found the overall survival for 3 and 5 years to be 47% and 24%, respectively, when metastatic disease was present. The 3- and 5-year survival rates improved to 60% and 30%, respectively, when no metastasis was present.[4] Another study showed that 30% of patients relapse, and of these patients, 20-25% survived, making it critical that cure rates are improved.[2]

The imaging of EES is different from that of bone ES since they originate from different sites. Although imaging is non-specific, EES tends to be well circumscribed and of generally low attenuation on CT. It is commonly hypoechoic on ultrasound and vascularity is variable.[4] Since this disease has a high rate of distant metastasis, the most common sites being lung and bone, it is suggested that chest radiograph or CT and bone scan be done before treatment to exclude distant metastasis and make a clinical stage with PET/CT holding promise for surveillance.

Conclusion

In conclusion, EES poses a diagnostic challenge for physicians. It is often mistaken for other neoplasms, which may delay diagnosis and worsen patient prognosis. Treatment includes neoadjuvant chemotherapy and wide surgical resection, followed by adjuvant chemotherapy and radiation. EES has a high rate of recurrence so surveillance imaging with PET/CT is recommended.

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