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Case Report

A Rare Orbital Growth Posing a Diagnostic Dilemma: Extraskeletal Ewing Sarcoma

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Abstract

Extraskeletal Ewing Sarcoma (EES) is a rare soft tissue tumor that rarely occurs in the head and neck region and closely resembles Ewing sarcoma of the bone in its histomorphology. We present a case of EES involving the lower eyelid of the right eye in a 28-year-old woman. The patient underwent wide local excision of the tumor. The atypical location of the lesion initially obscured the diagnosis, which was ultimately confirmed through immunohistochemical analysis.

Keywords: Extraskeletal Ewing sarcoma, soft tissue tumor, lower eyelid, primitive neuroectodermal tumor, Immunohistochemistry.

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INTRODUCTION

Ewing sarcoma family of tumours (ESFTs) comprises of a group of neoplasms which originate as a result of common genetic mechanisms, characterized by small round blue constituent cells. The members of this group include the classic Ewing sarcoma of the bone (ESB), extraskeletal Ewing sarcoma (EES), peripheral primitive neuroectodermal tumours (pNET) and Askin tumour of the chest wall [1]. While the classic Ewing sarcoma is the second most frequent bone sarcoma amongst children, the extraskeletal component of the same is a relatively rarer entity, accounting for about 6-47% of cases of all ESFTs [2]. It is an aggressive tumour, occurring with greater frequency in adolescents and young adults, with a tendency to metastasize.

CASE REPORT

A 28-year-old female presented to the outpatient unit of the Department of Ophthalmology with the complaint of swelling of the right lower lid. Physical examination showed a round non-tender swelling involving the right lower lid. The lower lid was easily retractable and revealed a round firm growth of size 1.8 x 1.5 cm, which appeared to arise from deeper orbital tissue. Engorgement of the overlying vessels was noted. Further detailed examination did not reveal any other abnormality of the eyeball, orbital space or eye movements. Head and neck computed tomography was carried out, which revealed a well-defined inferior orbital growth measuring 16x 19x 11 mm. MR brain and orbital imaging findings were suggestive of a solid homogenous enhancing intraconal mass lesion with small extraconal extension involving lower part of orbit, appearing in close relation with right inferior oblique muscle with few small cystic areas with it. No diagnostic abnormality was noted in the brain parenchyma.

Wide local excision of the tumour was performed and was found to be cystic, containing brown gelatinous material. The remainder of the cyst wall obtained was sent for histopathological assessment. The tissue received was creamish brown, soft to firm in consistency, measuring 2 x 1.5 x 1cm. On histopathological examination, the growth was found to be composed of a dual population of cells, one being monomorphic small round cells with increased N:C ratio, nuclear pleomorphism, coarse granular chromatin with prominent nucleoli and scant cytoplasm while the other population comprised relatively larger cells with irregular nuclear membrane and moderate eosinophilic cytoplasm (Figure 1A & B). The cells were arranged in the form of infiltrating sheets and nodules, separated by fibrous septa. Brisk mitotic activity with around 6 mitotic figures/10 hpf was noted. Extensive areas of necrosis with mixed inflammatory infiltrate were also present (Figure 1 C).

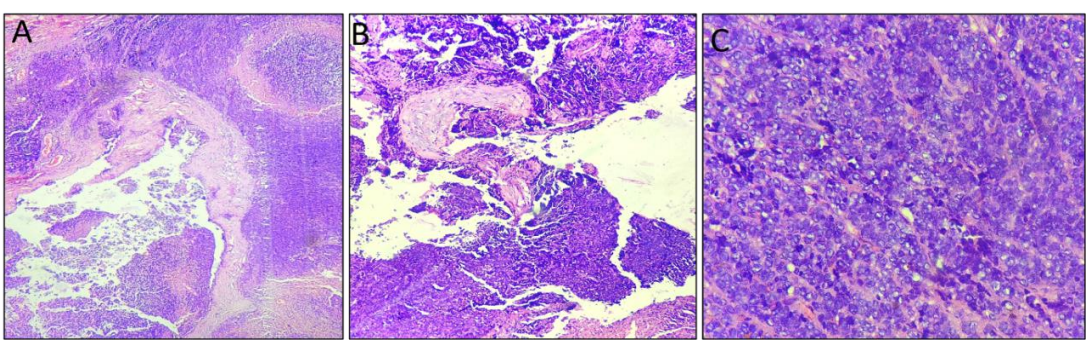

Figure 1: (A) H&E x 40, showing diffusely infiltrating tumor cells arranged in sheets and islands along with fibrocollagenous stroma and focal areas of necrosis. (B) H&E x100, showing diffusely infiltrating small round tumor cells showing a high N:C ratio with scant cytoplasm. (C) H&E x 400, showing sheets of small round blue cells having a very high N:C ratio, with fine to coarse chromatin and a scant amount of cytoplasm, separated by thin fibrous septa. Few mitotic figures were also noticed.

Based on the above histopathological findings and in conjunction with clinical and radiological findings, an initial probable diagnosis of Small round blue cell neoplasm was made, under which the following differentials were considered: Ewings's sarcoma, lymphoma, epithelioid angiosarcoma, neuroendocrine tumour and poorly differentiated carcinoma. To arrive at a more specific diagnosis, an appropriate IHC panel was advised which included CD 99, NKX2.2, FLI1, CD 117, PanCK, EMA, Ki67, CD45 (LCA), CD34, p63, NSE, chromogranin and S100. Non-reactivity of tumour cells to CD45 excluded lymphoma, whereas non-reactivity to chromogranin eliminated neuroendocrine tumour (Figure 2 A-I). Tumour cells were also found to be non-immunoreactive to CD34, PanCK and EMA, which led to the omission of both epithelioid angiosarcoma and poorly differentiated carcinoma. The tumour cells show strong membranous immunoreactivity for CD99, whereas patchy membranous positivity was noted for CD117. Similarly, immunoreactivity was also found for NSE, NXK2.2, S100 and p63, all of which are a part of the immunohistochemical panel for Ewing's sarcoma. Immunohistochemistry was, however, negative for FLI1. FLI1 is a member of the ETS family of transcription factors. About 80 to 90% of Ewing's sarcoma/pNET are characterized by the presence of the translocation t(11;22)(q24;q12) which results in EWS/FLI1 fusion gene, leading to the production of FLI1 protein which can be detected using antibody directed against the same.[1] The remainder 10-15% of Ewing's sarcomas carry fewer other rare forms of fusion genes, which may explain the non-reactivity of the tumour cells to FLI1 in our case. Ki67 index was high, approximately 60-70%, showing a high proliferative index, thereby confirming the high-grade nature of the tumour.

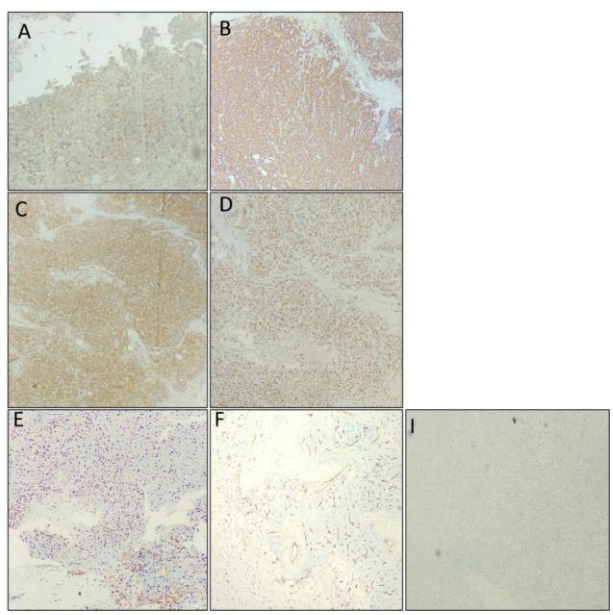

Figure 2 (A) IHC CD117; 100x, showing weak patchy membranous positivity in tumour cells. (B) IHC CD99; 100x, showing strong diffuse membranous positivity in tumour cells. (C) IHC NSE; 100x, showing diffuse cytoplasmic positivity in tumour cells. (D) IHC p63; 100x, showing diffuse nuclear positivity in tumour cells. (E) IHC Ki67; 100x, showing high proliferation rate ~ 60% (F) IHC CD34; 100x, showing non-reactivity in tumour cells while showing positivity in vessels which serve as internal control. (I) IHC PanCK; 100x, showing non-reactivity in tumour cells.

DISCUSSION

EES is a rare highly aggressive malignant neoplasm of mesenchymal origin, occurring more frequently amongst young adults with a slight male predominance. These tumours arise more commonly in the upper thigh, upper arm, buttocks and shoulder, whereas occurrence in the head and neck region, although

reported, is relatively rare, accounting for only 5-11 % of the cases [3]. Clinically, the symptoms may vary greatly depending on the site and extent of involvement, resulting in delay in diagnosis and targeted therapy. These tumours are rapidly growing masses, which may or may not be accompanied by tenderness, pain or other inflammatory signs [1].

Although osseous Ewing's sarcoma, both primary and metastatic, has been described in the orbit, EES arising from the orbit has rarely been reported. On reviewing existing literature, we found only 3 cases of primary orbital EES documented thus far. Li et al reported a case of primary orbital EES in a 56-year-old man, who presented with right upper eyelid swelling, diplopia, dizziness and headache [4]. Another case of a 14 year old boy who complained of a painless subconjunctival mass with history of sudden enlargement, was described by Lane et al [5]. Lastly, Alio et al reported the case of a 40 year old man who presented with painless progressive loss of vision and mild axial proptosis of right eye [6].

Radiological assessment is necessary to corroborate diagnosis, as well as to stage and monitor disease progression. Ultrasonography, computed tomography or magnetic resonance imaging may all be employed for the same, although none of the modalities provide with any pathognomonic findings for EES. On ultrasonography, EES may present as heterogenous mass of low echogenicity. On unenhanced CT examination, well demarcated growth of low attenuation is found. Administration of contrast lead to heterogenous enhancement in a fraction of the patients, along with localization of areas of increased vascularity, necrosis and calcifications [7]. MR imaging produces low to intermediate signal intensity on T1-weighted images and high signal intensity in T2-weighted images. Due the known propensity of EES to metastasize, a combination of CT thorax and abdomen, bone scan and FDG-PET can be utilized to assess the spread of disease. FDG-PET can also be employed to detect disease recurrence and gauge response to chemotherapy [8].

The histopathological features of the EES bear strong resemblance to other small round blue cell tumours, thereby leading to unavoidable dilemma in reaching a conclusive diagnosis. They consist of mononuclear uniform small round cells with spherical nuclei, inconspicuous nucleoli and scant cytoplasm, accompanied by areas of haemorrhage and necrosis. Mitotic activity is generally found to be low. Immunohistochemistry is utilized as an adjunct to supplement the histological analysis. Since no single marker is specific for EES, a panel that includes CD99, NXK2.2, CD117, S-100, synaptophysin and neuron-specific enolase is applied. Previous studies have reported positive immunoreactivity to CD99 in 90-95%, to CD117 in upto 65% of the cases and to NSE in 50-60% [8]. The vital role of the NXK2.2 protein in Ewing sarcoma oncogenesis has also been demonstrated by previous studies. NXK2.2 belongs to the NK2 family of transcription factors and is involved in cellular development in central nervous as well as endocrine systems. Expression of NXK2.2 protein at the cellular level has been detected immunohistochemically in about 90% of the cases of Ewing's sarcoma. Similarly, an antibody to FLI1 protein, which is the product of EWS/FLI1 fusion gene, has also been recently put into use.[9]

Genetically, cases of Ewing sarcoma are characterized by the presence of two chromosomal translocations: t(11:22)(q24:q12) and t(11:22)(q22:q12). These result in EWSR1-FLI1 (85-90%) and EWSR1-ERG (5-10 %) fusion genes respectively. Other rarer fusion genes have also been reported, most of which involve ESWR1 gene on chromosome 22. These can be demonstrated using reverse transcriptase (RT) PCR or fluorescence in-situ-hybridization (FISH) [10].

Due to the rarity of the occurrence of this tumour, modalities of treatment that can be employed have been studied in less detail. Localized EES is primarily treated by wide local excision. When it is not possible to achieve wide margins due to larger size or central location of the tumour, postoperative radiotherapy may be implemented [10]. Prior studies have also established that adjuvant and neoadjuvant chemotherapy can increase 5-year survival rate to up to 65%, along with eliminating metastases and preventing recurrences following excision [7,10].

CONCLUSION

EES is a rare tumour that can be suspected in younger patients presenting with a heterogeneous mass. Due to the variety of locations at which this tumour has been reported, the clinician needs to include it while

generating a list of relevant differential diagnosis. In the case presented above, we aim to highlight the unusual presentation as well as the approach towards diagnostic workup of an uncommon tumour. Along with maintaining a high index of suspicion, judicious use of radiological, histopathological and immunohistochemical assessment is imperative for arriving at the diagnosis.

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Conflicts of interest
There are no conflicts of interest

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