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Extraskeletal Ewing sarcoma of the parapharyngeal space with a unique translocation, t(19;22) (q13.4;q12.2)

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Abstract Extraskeletal Ewing sarcomas of the parapharyngeal space are extremely rare. It has been documented that Ewing sarcomas are morphologically and molecularly indistinguishable regardless of the tissue of origin. Around 85% of Ewing sarcomas are associated with translocation t(11;22)(q24.1;12.2) generating the EWSR1–FLI1 fusion oncoprotein. We report a case of an extraskeletal Ewing sarcoma arising in the parapharyngeal space with a unique translocation: t(19; 22) (q13.4;q12.2). To our knowledge this is the first case of an extraskeletal Ewing sarcoma exhibiting this translocation.

1. Introduction

Ewing sarcoma (ES) is a member of the Ewing sarcoma family of tumors (ESFT), which is a group of small round blue cell neoplasms comprising the second most frequent primary bone malignancy in children and young adults [1]. ESFT include ES, primitive neuroectodermal tumor (PNET), and Askin's tumor [2]. Approximately 15% of ES may arise in extra osseous sites [3,4] which rarely include the head and neck region [4]. Extraskeletal Ewing sarcoma (EES) most commonly occurs in the trunk or extremities and has no sex predilection [1]. Regardless the tissue of origin, ES is morphologically and molecularly indistinguishable [5].

Approximately 90% of ES cases demonstrate the translocation t(11;22)(q24.1;q12.2) creating a fusion gene between EWSR1 and FLI1, a member of the ETS family of transcription factors [6]. Most of the remaining 5%–10% of cases demonstrate a fusion between EWSR1 and ERG, which is another ETS family transcription factor located on chromosome 21q22.3 [6]. Other translocations are rare and are mainly described as fusions between EWSR1 or EWSR1-related genes and other ETS family transcription factors, such as ETV1, EIAF

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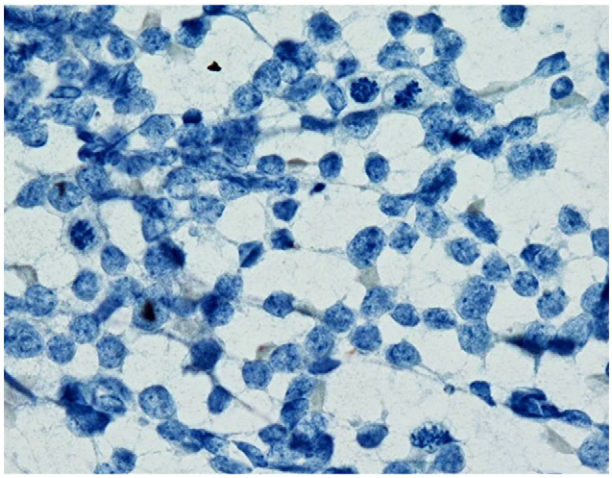

Fig. 1 Fine needle aspiration specimen showing clustered and single cells with round to oval nuclei, granular chromatin and mitotic figures.

(ETV4) and FEV [3,6]. The most frequently reported alternate translocations are t(7;22)(p22;q12.2) (EWSR1/ETV1), t(2;21;22)(q33;q22;q12.2) (EWSR1/FEV) and t(17;22)(q12;q12.2) (EWSR1/E1AF) [3].

2. Case report

A 23 year old female presented with a rapidly enlarging mass of the left parapharyngeal space. MRI of the orbits, face and neck revealed a 4.0 cm heterogeneously enhancing mass in the left carotid space, displacing the carotid bifurcation anteriorly. Fine needle aspiration (FNA) biopsy demonstrated evidence of a neoplasm showing clustered and single cells with round to oval nuclei, granular chromatin, few nucleoli, scanty cytoplasm, abundant mitotic figures and degenerated nuclei suggestive of a high-grade neoplasm (Fig. 1). The differential diagnosis included a poorly differentiated carcinoma, undifferentiated carcinoma, and poorly differentiated acinic cell carcinoma. Immunostains for chromogranin, synaptophysin, AE1/AE3, CD34, leukocyte common antigen, HMB-45, and smooth muscle actin were negative. S100 showed focal staining but this did not assist in further classification of this lesion. The needle rinse material from the FNA specimen was evaluated with flow cytometry and a lymphoma diagnosis was ruled out.

An incisional biopsy of the mass was diagnosed as small round blue cell malignant neoplasm. Immunohistochemical staining demonstrated strong positivity for S100, CD56 and vimentin and weak membranous staining of O13 (CD99) which was initially interpreted as negative. The tumor cells were negative for multiple cytokeratins (CAM5.2, AE1:AE3 and CK903), muscle markers (myoD1 and myogenin), neuroendocrine markers (neuron specific enolase, chromogranin and synaptophysin), vascular markers (CD31 and CD34) as well as leukocyte common antigen (CD45) and the melanoma marker Melan A. While the tumor had a neuroectodermal-type appearance, the weak O13 immunostain did not support the classification as PNET/Ewing sarcoma.

The patient was taken to the operating room for excision of the mass and a level I–IV left neck dissection. The mass involved the left vagus nerve, jugular vein, and the muscles of the floor of the neck but was completely excised without complications (Fig. 2). Histopathological examination revealed a small round blue cell neoplasm with multiple foci of perineural invasion involving the sympathetic chain, and metastasis to two cervical lymph nodes at levels 2 and 3. The tumor was strongly positive for S100 and focally positive for synaptophysin and O13 (CD99), while the following stains were negative: cytokeratins (CAM5.2 and AE1:AE3), muscle markers (muscle specific actin, myoD1, myogenin, calponin and caldesmon), neuroendocrine markers (neuron specific enolase, neurophilament, chromogranin and synaptophysin), as well as Leu-7 (CD57), CK20 and the melanoma markers (Melan A and human melanoma black), supporting the diagnosis of PNET/ES. The chromosome analysis of the resected tumor showed a t(19; 22)(q13.4;q12.2) confirmed by fluorescence in situ hybridization (FISH) analysis using ZNF443 (19p13.13), CRX (19q13.3) and

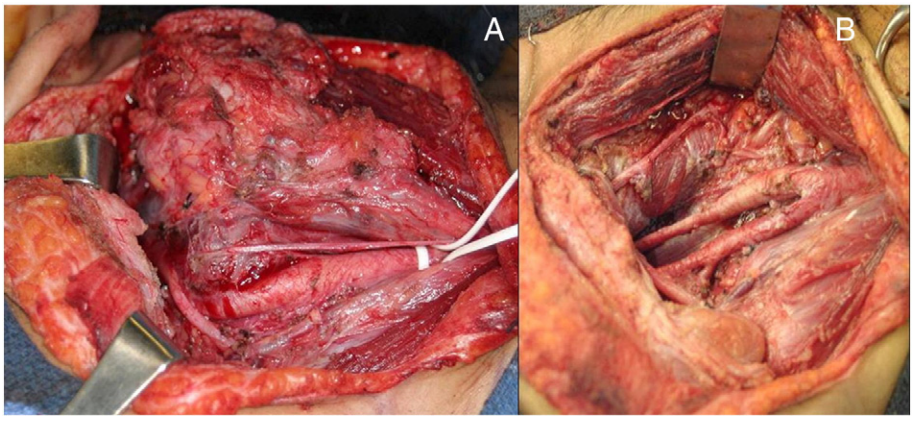

Fig. 2 Resection of parapharyngeal mass. Pre-operative picture showing the tumor between the carotid artery and the jugular vein with the vagus nerve entering the mass (A). Post-operative picture after resection of the mass, vagus nerve and jugular vein showing the preserved carotid artery (B).

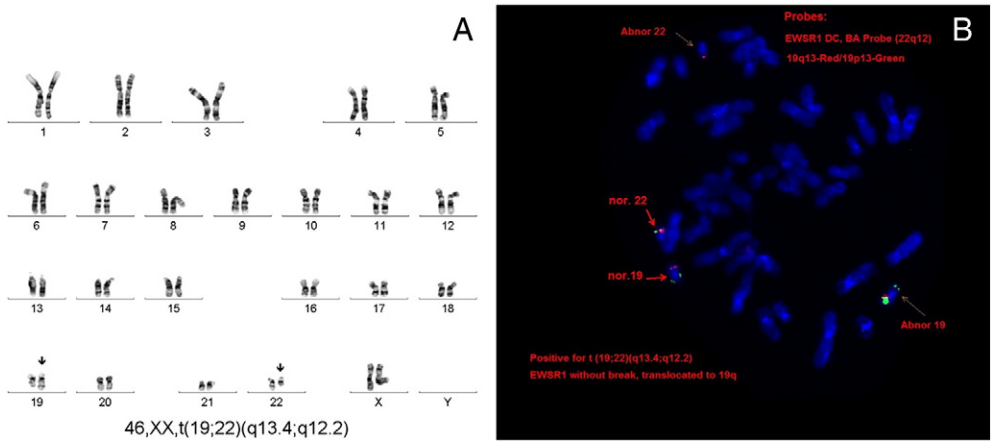

Fig. 3 Cytogenetic studies. GTG banded karyotype showing the t(19;22)(q13.4;q12.2) (A). Fluorescence in situ hybridization (FISH) analysis image shows EWSR1 translocated on to the 19q13.4 region (B).

the EWSR1 (22q12.2) locus specific unique sequence DNA probes (Fig. 3) [7]. Bone marrow chromosome analysis and FISH analysis were normal. The patient was treated with chemotherapy as per protocol COG AEWS0031 regimen B2 followed by autologous stem cell transplant. The patient expired 14 months after excision due to an intra-cerebral hemorrhage in the left parieto-occipital region with subfalcine and tonsillar herniation secondary to coagulopathy. This event occurred four days after stem cell rescue with high dose consolidation chemotherapy. The autopsy revealed no evidence of recurrent or residual neoplasm.

3. Discussion

Extraskeletal Ewing sarcoma (EES) are rare tumors of predominantly adolescents and young adults, most commonly presenting between the ages of 10 to 30 years, however they have been reported in children and older adults as well. EES of the head and neck accounts for approximately 4% of all EES. Few cases of parapharyngeal space ES have been reported. One case report presented a 53 year old Chinese man who was solely treated with chemotherapy and died of the disease 6 months after presentation [4]. A second case reported a 6 year old male with a right parapharyngeal space ES who was treated with chemotherapy and radiation with no evidence of recurrence 10 months post-treatment [8]. For both cases, the diagnosis was made based on a combination of morphology and immunohistochemistry, therefore the specific translocation in these cases is unknown. The 10 year survival rate of head and neck ES has been reported to be about 60%, which is similar to other sites of origin [9].

To our knowledge this is the first report of ES with a translocation involving 19q13.4. The chromosome band 19q13.4 has been implicated in other diseases and neoplasms in the past. Five case reports of hepatic mesenchymal hamartoma with chromosomal translocation involving the 19q13.4 breakpoint were published suggesting that this genetic region plays a role in the genesis of this lesion [10]. Mutations in this region has also been identified in a family with a form of cerebellar ataxia with autosomal dominant inheritance of a 19q13.4 mutation where the mutated region overlaps with the locus of spinocerebellar ataxia type 14 (SCA14), resulting in a mutation of protein kinase C gamma (PRKCG) [11]. A case of radiation-associated acute myeloid leukemia (AML) with a t(19;21)(q13.4;q22) translocation involving the AML1 gene has also been reported [12]. Additionally, t(19;22)(q13;q12) anomaly leading to a novel fusion EWSR1–ZNF444 was reported in a 40 year old female patient with myoepithelial carcinoma [13]. The ZNF444 gene was localized to 19q13.43. It should also be noted that the TNNT1 gene (Troponin T1, skeletal, Slow- GRCh37) has been localized to chromosome band region 19q13.4. TNNT1 encodes the slow skeletal muscle troponin. Mutations of TNNT1 leading to a truncated protein results in elimination of the C-terminal T2 domain that interacts with troponin C, I and tropomyosin [14].

As a small round blue cell tumor, the differential diagnosis of ES is broad with the final diagnosis relying on a combination of immunohistochemistry and cytogenetic analysis. The vast majority of EWS demonstrate strong membranous staining with O13 (CD99), which has also been reported in the EWS-ERG fusion [15]. In this case there was only weak membranous staining with O13 (CD99) which made the diagnosis more difficult. Only after the cytogenetic testing revealed that a translocation including the EWS R1 gene was the diagnosis of ES established in our patient. Other immunohistochemical stains that can be useful in establishing a diagnosis of ES are FLI1, which is positive in greater than 90% of ES, high molecular weight cytokeratins which are positive in only 5% of tumors, and desmin which is positive in 2% of cases [15].

Identification of specific translocations in tumors is becoming increasingly important, not only for diagnostic purposes but for therapeutic reasons as well. Recent work has characterized many of the transcriptional targets of the EWSR1–FLI1 gene, some of which already have known targeted chemotherapeutics available. Transcriptional targets have been identified in the Notch, Hedgehog/GLI, Wnt/

β-catenin, transforming growth factor β and IGF-1 receptor (IGF-1R) pathways among others [6]. Identification of potential transcriptional targets in the IGFR-1R pathway has possibly been the most important finding to date since it has led to several clinical trials of IGFR-1R inhibitors which have been shown to have some benefit in a subset of patients [6]. More work is needed to determine if there are important differences in the affected pathways of ES cases with alternate translocations.

In conclusion, rare translocations in ES have the potential to aid in the diagnosis and are valuable for correct tumor classification and therapeutic purposes. Although t(11;22)(q24.1;q12.2) anomaly is the hallmark of ES, the fusion product of EWS–FLI1 genes by itself does not transform human cells and other co-operating mutations may appear to be necessary to understand the cell origin of ES. Further studies as well are needed to determine the importance of the chromosome band 19q13.4 involvement in ES and other malignancies.

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