

Background

- EWSR1::CREM* (Ewing sarcoma breakpoint region 1::cAMP response element modulator) gene fusions are rare, occurring in a variety of tumors, including intracranial myxoid mesenchymal tumor, hyalinizing clear cell carcinoma of the head and neck, clear cell sarcoma, and angiomatoid fibrous histiocytoma.
- Our study expands the spectrum of *EWSR1::CREM*-rearranged tumors, describing three cases of squamous cell carcinoma (SCC) of the thorax and head and neck that encode this gene fusion.

Design

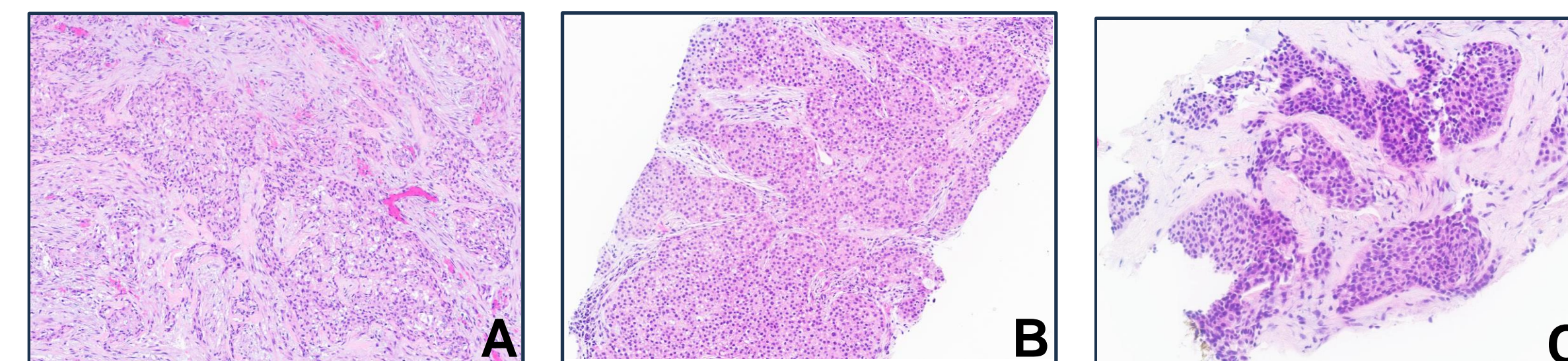
- Paraffin-embedded tumor samples underwent DNA (592-gene or whole exome) and RNA (whole transcriptome) sequencing at Caris Life Sciences (Phoenix, AZ).
- Fusion transcripts, including *EWSR1::CREM* rearrangements, were detected by whole transcriptome sequencing.
- Pathologists (MGE, AER) confirmed diagnoses, and treatment and outcome data were extracted from patient medical records.

Results

- EWSR1::CREM* rearrangement was detected in 18 tumors (see Table 1.0):
 - 5 malignant epithelioid neoplasms with predilection for mesothelial-lined cavities,
 - 4 hyalinizing clear cell carcinomas,
 - 3 non-keratinizing SCCs,
 - 2 clear cell sarcomas,
 - 2 small round and spindle cell sarcomas,
 - 1 intracranial myxoid mesenchymal tumor, and
 - 1 mesothelioma.

Table 1.0 and Figure 1A/B/C

SPECTRUM OF <i>EWSR1::CREM</i> - REARRANGED TUMORS						
#	AGE	GENDER	LOCATION	DETECTED FUSION	OTHER FINDINGS	DIAGNOSIS
				<i>EWSR1</i> (exon 7)		
1	36	Male	Cervical spine	:: <i>CREM</i> (exon 6)	None	Epithelioid neoplasm with <i>EWSR1::CREM</i> fusion
				<i>EWSR1</i> (exon 13)		
2	26	Male	Kidney	:: <i>CREM</i> (exon 6)	None	Epithelioid neoplasm with <i>EWSR1::CREM</i> fusion
			Liver and	<i>EWSR1</i> (exon 13)		
3	21	Female	adrenal	:: <i>CREM</i> (exon 6)	None	Epithelioid neoplasm with <i>EWSR1::CREM</i> fusion
				<i>EWSR1</i> (exon 13)		
4	37	Female	Liver	:: <i>CREM</i> (exon 5)	None	Epithelioid neoplasm with <i>EWSR1::CREM</i> fusion
				<i>EWSR1</i> (exon 7)		
5	30	Female	Uterus	:: <i>CREM</i> (exon 6)	None	Epithelioid neoplasm with <i>EWSR1::CREM</i> fusion
				<i>EWSR1</i> (exon 15)		
6	76	Male	Maxilla	:: <i>CREM</i> (exon 6)	None	Hyalinizing clear cell carcinoma
				<i>EWSR1</i> (exon 13)		
7	77	Male	Mandible	:: <i>CREM</i> (exon 5)	None	Hyalinizing clear cell carcinoma
				<i>EWSR1</i> (exon 13)		
8	13	Female	Salivary gland	:: <i>CREM</i> (exon 6)	None	Hyalinizing clear cell carcinoma
				<i>EWSR1</i> (exon 10)		
9	57	Male	Skull base	:: <i>CREM</i> (exon 5)	None	Hyalinizing clear cell carcinoma
				<i>EWSR1</i> (exon 13)		
10	62	Female	Lung	:: <i>CREM</i> (exon 6)	None	Squamous cell carcinoma
				<i>EWSR1</i> (exon 13)		
11	37	Female	Oropharynx	:: <i>CREM</i> (exon 6)	None	Squamous cell carcinoma
			Maxillary	<i>EWSR1</i> (exon 8)		
12	51	Male	sinus	:: <i>CREM</i> (exon 4)	<i>NF2</i> p.E527*	Squamous cell carcinoma
				<i>EWSR1</i> (exon 7)		
13	43	Male	Skin	:: <i>CREM</i> (exon 6)	None	Clear cell sarcoma
			Transverse	<i>EWSR1</i> (exon 13)		
14	44	Male	colon	:: <i>CREM</i> (exon 6)	None	Clear cell sarcoma
			Rectus	<i>EWSR1</i> (exon 7)		
15	50	Male	muscle	:: <i>CREM</i> (exon 6)	None	Small round and spindle cell sarcoma
				<i>EWSR1</i> (exon 10)		
16	75	Female	Small bowel	:: <i>CREM</i> (exon 6)	None	Small round and spindle cell sarcoma
				<i>EWSR1</i> (exon 7)		
17	75	Male	Brain	:: <i>CREM</i> (exon 6)	None	Intracranial myxoid mesenchymal tumor
				<i>EWSR1</i> (exon 13)		
18	28	Female	Peritoneum	:: <i>CREM</i> (exon 6)	None	Epithelioid mesothelioma



Squamous Cell Carcinoma and *EWSR1::CREM*

- Patient 10, a 62-year-old female with SCC originating from the lung, achieved 5-year complete remission after resection and adjuvant chemotherapy (tumor shown in Figure 1A).
- Patient 11, a 37-year-old female, presented with oropharyngeal SCC. This patient underwent aggressive chemoradiation due to metastasis to lymph nodes and lungs (tumor shown in Figure 1B).
- Patient 12, a 51-year-old male, had SCC in the maxillary sinus. Similar to Patient 11, chemoradiation was administered given involvement of lymph nodes and lungs (tumor shown in Figure 1C).
- At 13 and 2 years of follow-up, respectively, both Patient 11 and Patient 12 are alive, with some radiographic evidence of disease progression while receiving intermittent systemic therapy.
- All three cases exhibited typical morphologic characteristics (i.e. intercellular bridges) and immunohistochemical profiles (i.e. keratin, p40/p63 positivity).

Conclusions

- Our study broadens the spectrum of tumors associated with *EWSR1::CREM* rearrangement and is the first to document its presence in SCCs of the lung and head and neck.
- While there is no specific standardized approach to treatment for patients whose tumors have these translocations, it is noteworthy that all three patients in this series are alive despite the presence of metastases and, in some instances, the absence of therapy over several years.
- Identification of additional cases will be helpful to better understand the disease course and optimal therapy of SCC harboring the *EWSR1::CREM* fusion.

References

- Campoverde L, Camacho F, Alessandrino F, Evans MG, Elliot A, Rosenberg A, Trent J. Case report: The activity of multi-kinase VEGF inhibitor, Pazopanib, in metastatic undifferentiated round cell sarcomas harboring *EWSR1::CREM* fusion: clinicopathological series of two cases and literature review. *Frontiers in oncology*. 2023;13.
- Kaprio H, Siddiqui A, Saustila L, Heuser VD, Gardberg M. The oncogenic properties of the *EWSR1::CREM* fusion gene are associated with polyamine metabolism. *Scientific Reports*. 2023 Mar 25;13(1):4884.



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