O-8

From Neuroendocrine Neoplasms to Sarcomas: How Genetic Testing Reveals Diagnostic Pitfalls

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BACKGROUND

Neuroendocrine neoplasms (NENs) are heterogeneous with wide range of histological differentiation. Chromogranin, synaptophysin, and INSM1 are commonly expressed in NEN. Round cell sarcomas, such as Ewing sarcoma (ES), and desmoplastic small round cell tumor (DSRCT), can overlap morphologically and immunohistochemically with NENs, complicating diagnosis. Herein, we describe four cases of high-grade NEN that were subsequently classified as round cell sarcoma.

METHODS

This single-institution case series retrospectively reviews four cases initially diagnosed as NENs and later identified as round cell sarcoma.

RESULTS

Three cases were originally diagnosed as neuroendocrine carcinoma (NEC) and one as a grade 3 well differentiated neuroendocrine tumor (G3 NET) (Table 1). All cases were referred from outside facility with further initial confirmation of pathology at our institution. Immunohistochemical (IHC) was positive for synaptophysin and chromogranin in all the cases except one (pt#4) where both stains were negative, but positive for INSM1 and CD56. Subsequent Next-Generation Sequencing (NGS) revealed genetic fusions indicative of round cell sarcomas: *EWSR1-WT1* in two cases, *EWSR1-FLI1* in one, and *EWSR1-PATZ1* in another, consistent with DSRCT, ES, and undifferentiated small round cell sarcoma, respectively. This led to treatment modifications in all patients except one who died shortly after the first dose of platinum and etoposide (EP). Interestingly, pt#1 and #3 had initial partial response to EP before quickly progressing thereafter.

Table 1: Summary of Cases

Case (Age/Sex)	Initial Dx/ subsequent Dx	Synaptophysin/ Chromogranin/INSM1	Ki-67 Index	Genetic Findings (method)
1 (33 M)	NEC/ES	+/-/+	~100%	EWSR1-FLI1 (Tissue and blood NGS AND FISH)
2 (63 F)	NEC/ undifferentiated round cell sarcoma	+/+/?	40%	EWSR1-PATZ1 (Tissue NGS)
3 (43 M)	NET G3/DSCRT	+/+/?	60%	EWSR1-WT1 (Tissue NGS)
4 (57 M)	NEC/DSCRT	-/-/?	80%	EWSR1-WT1 (Tissue NGS)

CONCLUSION

Sarcomas can express NET markers and be misdiagnosed as NENs. This case series underscores the critical role of NGS in the accurate diagnosis of NEN mimickers, which can significantly alter treatment decisions and outcomes.

ABSTRACT ID 28611