(Mammary Analogue) Secretory Carcinoma of the Nasal Cavity: Report of a Rare Case with p63 and DOG1 Expression and Uncommon Exon 4–Exon 14 *ETV6-NTRK3* Fusion Diagnosed with Next Generation Sequencing

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Received: 22 April 2019 / Accepted: 28 June 2019 / Published online: 4 July 2019
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Abstract

We present a 72 years old male with a left nasal cavity (mammary analogue) secretory carcinoma (SC) which exhibited classical morphological features on light microscopical examination, diffuse strong S100 and mammoglobin positivity on immunohistochemistry, and *ETV6-NTRK3* gene fusion on next generation sequencing (NGS) analysis. Unusual features of this tumor are expression of p63 and DOG1 on immunohistochemistry and the atypical junction between Exon 4 of the *ETV6* gene and Exon 14 of the *NTRK3* gene.

Keywords Mammary analogue secretory carcinoma · Nasal cavity · Immunohistochemistry · *ETV6-NTRK3* fusion protein, human

Introduction

(Mammary analogue) Secretory carcinoma (SC) was first described in 2010 by Skalova et al. in a series of 16 tumors from the parotid gland and minor salivary glands of the oral cavity, with histomorphologic and immunohistochemical features strongly reminiscent of secretory carcinoma of the breast [1]. On immunohistochemistry, SC is typically positive for S100 protein, mammoglobin, GATA3, STAT5 and MUC4, but negative for p63 and DOG1 [2–4]. Like secretory carcinoma of the breast, salivary gland SC typically demonstrates a t(12;15) (p13; q25) *ETV6-NTRK3* translocation. Classically, the junction is between Exon 5

of *ETV6* and Exon 15 of *NTRK3*. Since the original series, SC has been subsequently reported in non-salivary gland sites such as skin, thyroid gland, eyelid, lung, as well as in the sinonasal tract [5–10]. Recently, bona fide salivary gland SC with *ETV6-RET* and *ETV6-MET* translocations have been described, thus expanding the molecular profile of SC beyond the *ETV6-NTRK3* translocation [11, 12]. The age range of SC is wide; while most cases occur in adults, with a mean age of about 45 years, pediatric cases have also been described [4, 13–15]. There is a slight predilection for males [4, 13].

Herein we report a case of a primary SC of the nasal cavity. To the best of our knowledge, only four cases of SC have been reported in the literature, including one case with high-grade transformation [7, 8]. The case we report is unusual in its immunohistochemical profile, being focally positive for p63 and DOG1, and also demonstrating an atypical junction between Exon 4 of *ETV6* and Exon 14 of *NTRK3*.

Case Report

The patient is a 72 year old male who had a previous endoscopic resection of left nasal cavity sphenopalatine area adenocarcinoma in 2004. Subsequently, he underwent right

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parotidectomy for mucoepidermoid carcinoma, intermediate grade, in 2015. The histology slides and paraffin blocks of both the left nasal cavity adenocarcinoma (from 2004), and the right parotid gland mucoepidermoid carcinoma (from 2015), were not available at our institution for review. The patient presented with intermittent blood-stained mucus from the nose. Nasal endoscopy revealed a small polypoid tumor at the posterior end of the left inferior turbinate stump, near the left sphenopalatine area, which corresponds to the site of the previous endoscopic resection (Fig. 1a). On magnetic resonance imaging (MRI), the lesion measured approximately 0.8 × 0.4 cm in size, and was confined to the nasal choana. An excision biopsy was performed.

Results

Histopathology

The tumor was composed of a combination of microcystic, papillary-cystic and solid architectural patterns (Fig. 1b–d). The lumina contain abundant eosinophilic colloid-like (PAS positive, diastase resistant) secretions (Fig. 1e). The tumor cells exhibited uniform, medium-sized, round to oval nuclei with occasional small single nucleoli and abundant, eosinophilic cytoplasm (Fig. 1f). The mitotic activity was inconspicuous. Tumor necrosis was absent.

Immunohistochemistry

The immunohistochemical study showed that the tumor cells diffusely expressed S100-protein, mammoglobin and GATA3 (Fig. 2a–c). The neoplastic cells displayed patchy nuclear expression of p63 throughout the tumour (approximately 20% of tumour cells are positive for P63), with no biphasic (luminal/abluminal) pattern. There is patchy tumour expression of DOG1 (incomplete membranous staining, mainly decorating glandular lumina). The tumour cells demonstrate patchy weak expression of SOX10 (nuclear staining) in a similar distribution as p63 (Fig. 2d–f). The Ki-67 proliferation index was approximately 10%.

Next Generation Sequencing (NGS)

Sample Preparation for NGS

For NGS testing, 3 formalin-fixed paraffin embedded (FFPE) Sections (10 µm thick) were macrodissected to isolate tumor-rich regions. Sample was extracted for total nucleic acid using Agencourt FormaPure Kit (Beckman Coulter, Brea, CA) following the corresponding protocol with an overnight digest and an additional 80 °C incubation as described in modification of the protocol by ArcherDX

(ArcherDX Inc., Boulder, CO). Total nucleic acid was quantified using the Qubit Broad Range RNA Assay Kit (Thermo Fisher Scientific).

RNA Integrity Assessment and Library Preparation for NGS

Input for NGS library preparation was 250 ng of FFPE RNA. To assess RNA quality, the PreSeq RNA QC Assay using iTaq Universal SYBR Green Supermix (Biorad, Hercules, CA) was performed to generate a measure of the integrity of RNA [in the form of a cycle threshold (Ct) value]. Library preparation and RNA QC was performed following the Archer Fusion Plex Protocol for Illumina (ArcherDX Inc.). The FusionPlex Solid tumor kit was used. Final libraries were diluted 1:100,000 and quantified in a 10 µL reaction following the Library Quantification for Illumina Libraries protocol and assuming a 200 bp fragment length (KAPA, Wilmington, MA).

NGS Sequencing and Data Analysis

Libraries were diluted to 4 nM and sequenced on a NextSeq sequencer (Illumina, San Diego, CA). The optimal number of raw reads per sample was set to 3,000,000. Library pools were diluted to 1,6 pM library stock with 20% 1,8 pM PhiX and loaded in the NextSeq cartridge. The fusion and other rearrangement detection algorithm in Archer Analysis relies on the specificity of the gene specific primers (GSPs) used in the amplification steps in the AMP process. The resulting FASTQ files were analyzed using the Archer Analysis software (v5; ArcherDX Inc.). Fusion parameters were set to a minimum of five valid fusion reads with a minimum of three unique start sites within the valid fusion reads.

NGS Findings

NGS revealed *ETV6-NTRK3* fusion, with junction between exon 4 of *ETV6* and exon 14 of *NTRK3* (Fig. 3). The read depth at the breakpoint was 1556 reads. The fusion is found in 38% of all reads detected at this site. 345 of the fusion-supporting reads had unique start sites.

Discussion

The sinonasal tract appears to be an uncommon site for SC, with only four previously reported cases thus far (Table 1) [7, 8, 16]. SC is characterized by *ETV6* translocation. While most cases of SC have *ETV6-NTRK3* translocation, a subset of published tumors demonstrated a *ETV6* gene split as visualized by fluorescence in situ hybridization (FISH), but in which the classical *ETV6-NTRK3* (exons 5–15) fusion transcript was not detected by reverse transcriptase polymerase

Fig. 1 **a** Endoscopic image of the recurrent tumor in the nasal cavity. **b** There is a microcystic pattern with abundant intra-luminal eosinophilic secretions. Hematoxylin and Eosin stain, $\times 20$ magnification. **c** A combination of microcystic and papillary-cystic patterns are seen. Hematoxylin and Eosin stain, $\times 100$ magnification, $\times 100$ magnification. **d** A combination of papillary-cystic and solid patterns are seen. Hematoxylin and Eosin stain, $\times 100$ magnification. **e** The abundant

intra-luminal secretions are positive for periodic acid-Schiff stain (following diastase pre-treatment). Periodic acid-Schiff stain (following diastase pre-treatment), $\times 100$ magnification. **f** The tumor cells exhibit round to oval, medium size nuclei with small nucleoli and ample eosinophilic cytoplasm. Hematoxylin and Eosin stain, $\times 400$ magnification

Fig. 2 **a** The tumor cells diffusely expressed S100. Immunohistochemistry, S100 antibody, $\times 200$ magnification. **b** The tumor cells diffusely expressed mammoglobin. Immunohistochemistry, mammoglobin antibody, $\times 100$ magnification. **c** The tumor cells diffusely expressed GATA3. Immunohistochemistry, GATA3 antibody, $\times 100$ magnification. **d** The tumor cells show patchy nuclear expression of p63 with no biphasic (luminal/abluminal) pattern. This pattern of staining was present throughout the tumor, and correlates with the

expression of SOX10. Immunohistochemistry, P63 antibody, $\times 400$ magnification. **e** The tumor cells show patchy expression of DOG1 (incomplete membranous staining, mainly decorating glandular lumina). Immunohistochemistry, DOG1 antibody, $\times 400$ magnification. **f** The tumor cells show patchy and weak expression of SOX10. This pattern of staining was present throughout the tumor, and correlates with the expression of p63. Immunohistochemistry, SOX10 antibody, $\times 400$ magnification

Fig. 3 Raw NGS data visualization of the ETV6-NTRK3 exons 4–14 fusion. The read depth at the breakpoint is 1556 reads. The fusion is found in 38% of all reads detected at this site. The fusion is supported by 345 reads with unique start sites

chain reaction (RT-PCR) [17]. A possibility is that there was truly an *ETV6-NTRK3* fusion, but that this was not detected by RT-PCR, possibly because of non-classical/atypical junctions, which was not targeted by RT-PCR. More sophisticated molecular techniques such as next generation sequencing could overcome the limitations of RT-PCR. For example, Baneckova et al. described a case of SC with non-classical/atypical *ETV6-NTRK3* exons 5–13 fusion, which was not detected by RT-PCR, but detected by Archer next generation sequencing [8]. Skalova et al. had also described four cases of SC with non-classical/atypical *ETV6-NTRK3* exons 4–14 fusion (detected with nested RT-PCR) [17]. SCs with *ETV6* break-apart but which truly lacked the *ETV6-NTRK3* rearrangement were termed to harbor *ETV6-X* gene fusion by

Skalova et al. and Ito et al., reflecting the uncertainty of the *ETV6* translocation partner in such cases [17, 18]. Recently, a case of SC with *ETV6-MET* fusion, and ten cases of SC with *ETV6-RET* fusions, were described [11, 12]. A case of skin MASC with *NFIX-PKN1* has also been reported [19]. A case of parotid gland MASC with dichotomous growth patterns demonstrating dual *ETV6-NTRK3* and *ETV6-MAML3* fusions was also published recently [20]. With these new developments, the molecular spectrum of SC has expanded beyond the *ETV6-NTRK3* gene fusion which was described in the original series by Skalova et al. [1].

ETV6 translocations, and *ETV6-NTRK3* gene fusions, are not unique to SC. *ETV6-NTRK3* translocation were initially described in infantile fibrosarcoma [21], and was

Table 1 Previously reported cases of sinonasal secretory carcinoma

Case No	Age (years)	Gender	Site	Molecular profile and detection method	Size	Lymph node or distant metastases	High-grade transformation	Treatment and outcome
1 [7]	67	Female	Left ethmoid sinus	ETV6-NTRK3 fusion (detected via FISH), junction not known	Not known	Not known	No	Not known
2 [16]	61	Male	Left maxillary sinus	ETV6 break-apart (detected via FISH), translocation partner not known	4.2 cm	No	Yes	Left maxillectomy and adjuvant radiation therapy No evidence of disease 8 months after resection
3 [8]	51	Female	Right nasal septum	ETV6-NTRK3 fusion (detected via next generation sequencing), atypical exon 5–exon 13 junction	1.5 cm	No	No	Resection No evidence of disease after more than 10 years of follow up
4 [8]	65	Female	Right nasal cavity	ETV6 and NTRK3 break-apart (detected via FISH)	4 cm	No	No	Resection and adjuvant radiation therapy No evidence of disease after 4 years of follow up

subsequently described in a variety of tumors, including secretory carcinoma of the breast [22], congenital mesoblastic nephroma [23], papillary thyroid carcinoma [24] and acute myeloid leukemia [25]. In the context of a low-grade, non-intestinal type adenocarcinoma of the sinonasal tract, *ETV6* translocation alone suggests the diagnosis of either SC or *ETV6* rearranged low-grade SNAC. The latter is a recently described entity that is characterized by *ETV6* gene fusions, often involving the *NTRK3* gene partner [26, 27]. As such, it has a similar/identical molecular profile as SC. However, these two entities have different morphological and immunohistochemical features.

SC typically exhibits solid, microcystic, papillary-cystic, tubular and cribriform patterns in varying proportions, with the microcystic and tubular components often containing abundant luminal eosinophilic (PAS positive and diastase resistant) secretions. There is usually variable infiltration into the surrounding tissue. A prominent fibrous stroma is often discerned within the tumor. In the absence of high-grade transformation, the tumor cells often possess relatively uniform round to oval nuclei with occasional small nucleoli and abundant eosinophilic cytoplasm [1, 13, 28, 29].

In contrast, the three cases of *ETV6* rearranged low-grade SNAC described by Andreasen et al. is well circumscribed with predominantly tubular architecture and with tumor cells containing small round monotonous nuclei [26]. Often there is scarce tumor stroma. While some of the lumina may also

contain eosinophilic secretions that are PAS positive and diastase resistant, this feature is not as prominent as in SC.

Immunohistochemically, SC typically shows strong diffuse expression for S100 protein, GATA3 and mamoglobin, but is negative for DOG1 [2, 13, 28]. In contrast, *ETV6* rearranged low-grade SNAC typically shows strong apical membranous staining with DOG1, with only scattered single cells and tumor clusters expressing S100 protein. Moreover, *ETV6* rearranged low-grade SNAC do not express mamoglobin, while GATA3 expression may be weak and focal [26].

In the original paper on SC by Skalova et al., there was no expression of basal cell/myoepithelial cell markers such as p63, calponin, CK14, smooth muscle actin and CK5/6 [1]. However, Laco et al. subsequently described two cases of SC with focal expression of p63. One case also expressed calponin, while the other case also expressed CD10 [4]. Our case exhibited patchy expression of p63. SC is typically negative for DOG1 membranous expression on immunohistochemistry. When present, DOG1 membranous expression is usually weak and limited to the periphery of tumour nests, or decorates the glandular lumina [2, 13]. This is in contrast to acinic cell carcinoma (AcCC), which typically demonstrates diffuse canicular DOG1 expression [13].

Most cases of SC have *ETV6-NTRK3* gene fusion, classically with exon 5 (of *ETV6*)–exon 15 (of *NTRK3*) junction. Atypical junctions include exon 4 (of *ETV6*)–exon 14 (of *NTRK3*), and exon 5 (of *ETV6*)–exon 15 (of *NTRK3*) [17].

Our case demonstrates atypical exon 4–exon 14 junction, which is uncommon (but not hitherto unknown). Skalova et al. observed a greater propensity for more aggressive behavior in SC with atypical junctions, as compared to SC with classical exon 5–exon 15 junction, although the number of cases published thus far is small [17].

In terms of prognosis, SC is regarded similar to AcCC, with no statistically significant mean disease-free survival for both entities [30]. Local recurrences, regional lymph node metastases and high-grade transformation with distant metastases leading to death may occur [29]. Interestingly, a case of sinonasal SC with high-grade transformation has been reported [16]. High-grade transformation is reflected in traditional histopathological features of malignancy such as brisk mitotic activity, necrosis and marked nuclear pleomorphism.

Importantly, *ETV6-NTRK3* rearranged SC may be treated with Trk inhibitors Entrectinib and larotrectinib [11]. Knowledge of the *ETV6* translocation partner is thus crucial, as it may guide targeted therapy.

In conclusion, we herein describe the clinicopathological features of the fifth patient with *ETV6-NTRK3* translocated SC of the nasal cavity. Our case is unusual in its expression of P63 and DOG1 on immunohistochemical study, as well as its atypical exon 4 (of *ETV6*)–exon 14 (of *NTRK3*) junction that was captured on NGS analysis.

Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest.

Ethical Approval It is our institution's policy not to require formal ethical approval for reports on up to two patients.

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