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CASE REPORT

SIALOBLASTOMA IN A NEWBORN: A DIAGNOSTIC CHALLENGE OF A RARE ENTITY

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ABSTRACT: Sialoblastoma is a rare epithelial tumor of the salivary glands with an uncertain potential for malignancy, which typically affects children. A 20-days-old female child was referred to the Department of Maxillofacial Surgery due to the presence of a large mass localized at the left lateral cervical region, near the mandibular angle. The physical and instrumental examinations revealed a large nodular mass occupying almost completely the left neck. The patient was submitted to surgery and the neoplasms was excised "en bloc". Histological examination showed a neoplastic proliferation of basaloid cells predominantly organized in solid nests. Immunohistochemistry study displayed expression of Pan Keratin and p63 with a Ki-67 homogeneous staining in about 20% of tumor cells. The prognostic role of Ki-67 proliferation index has been suggested with low value (<5%) associated with a good prognosis without disease recurrence. Through this case and the review of the literature we try to establish the state of the art regarding the clinical aspects, the morphological and immunophenotypic features for diagnostic purpose. Moreover, we asses which parameters can influence the prognosis, paying attention especially to the cases of sialoblastoma diagnosed in the first year of life.

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Impact statement: The case we presented demonstrates that rare masses in newborns can be challenging to diagnose due to their rarity, but in this clinical context, they are expected to have a favorable prognosis.

Key words: *sialoblastoma; newborn; salivary gland neoplasm; Ki67.*

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INTRODUCTION

The occurrence of a head and neck tumoral mass at birth or shortly afterwards may cause concern and the differential diagnosis may be challenging. Indeed, clinical, instrumental and pathological examinations are needed to obtain an exact diagnosis, as the differential diagnosis is wide. Particularly, salivary gland tumors are rare in pediatric age, accounting for less than 5% of all the cases, with an annual incidence of 0.8 per million (1, 2). The occurrence of salivary gland tumors in newborn is anecdotical, as less than 0.25% of all cases are diagnosed in the first decade of life (3). In this field, there is a little consensus about the diagnostic and therapeutic management of sialoblastoma, due to its rarity and the considerably variable clinical behavior (4, 5). Sialoblastoma is an exceptionally uncommon epithelial salivary gland tumors with uncertain potential of malignancy, most common occurring in infancy (2). It was defined as a tumor resembling epithelial anlage of salivary glands but in arrested state of differentiation (6). The most common loca-

tion is the parotid gland, while only occasional cases have been reported in the submandibular gland (4). Most cases are diagnosed at birth or shortly afterwards, but rarely it could be identified later (7, 8). Sialoblastoma typically shows solid organoid nests of primitive basaloid epithelial cells, separated by dense fibrous stroma. Neoplastic cells are characterized by scant cytoplasm and large, round to oval, nuclei with high nuclear to cytoplasmic ratio, with occasionally peripheral nuclear palisading. Images of ductal structures lined by cuboidal to columnar epithelium with intraluminal basophilic secretions or a cribriform architecture may be observed (8-10). Neoplastic cells are invariably positive for SOX10, p63 and β-catenin and variably positive for cytokeratin (such as CK5/6, CK7 and CK19), S100, smooth muscle actin, c-kit (CD117) and calponin by immunohistochemistry (11, 12).

Interestingly, p63 immunostaining appears non-homogeneously positive in the neoplasm with protein expression typically in basaloid cells and it would represent a marker of undifferentiation of these cells. In this regard, sialoblastoma generally shows a more intense p63 expression in the peripheral cells of the solid tumor nests, rather than in the center of the nest. This evidence should be an expression of the progressive differentiation of basaloid cells (12). The histological and immunohistochemical features and the young age allow to differentiate this neoplasm from others basaloid tumors, such as basal cell adenoma/adenocarcinoma, adenoid cystic carcinoma, and adamantinoma-like Ewing sarcoma (13). Eighty cases of sialoblastoma have been reported in the literature at the best of our knowledge, with a prevalence of these identified within the first year of life. Clinical and pathological details of the previous reported cases are reported in **Table 1** (2, 14-49). More specifically, 48 cases (63.75%) were diagnosed in the first year of life, while the remaining 29 cases (36.15%) were discovered after the first year. Regarding the cases identified within the first year, 33 out of 48 cases (68.75%) were diagnosed in the first month of life and the parotid gland was the prevalent site of onset with 36 out of 48 cases (75%). Twelve out of 48 (25%) cases have arisen in the submandibular gland. Instead, sialoblastoma originating in the minor salivary glands are exceptionally rare as only 2 out of 48 cases (4.16%) have been reported. One case out of 48 (2.08%) has been described arising in an ectopic salivary gland. Moreover, the incidence of the neoplasm is almost equal in the male (23 cases out of 48 (47.9%)) and female (21 out of 48 cases (43.75%)). The gender was not reported in 4 out of 48 cases (10%).

CLINICAL REPORT

A 20-days-old female child was referred to the Department of Maxillofacial Surgery due to the presence, at the birth, of a large mass localized at the left lateral cervical region, near the mandibular angle. The physical examination revealed a large nodular mass with a diameter of about 10 centimeters, occupying almost completely the left neck. Instrumental examinations were performed, including X-Rays and nuclear magnetic resonance (NMR). Particularly, X-Rays showed that the neoplasm did not contract anatomical relationships with the cervical ribs (**Figure 1A**), while NMR re-

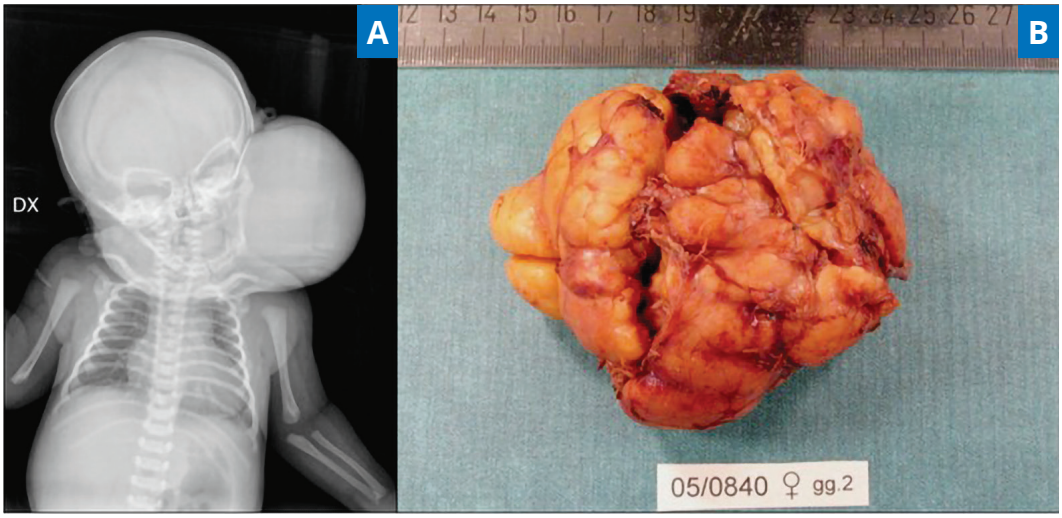

Figure 1. ***(A)*** *X-Rays showing a large mass occupying the left neck, without erosion of the maxillary bone;* ***(B)*** *surgical specimen consisting in an irregular but well-circumscribed nodular mass with a diameter of 9 centimeters.*

Table 1. *Sialoblastomas diagnosed in the first year of life: review of the literature.*

REFERENCES	N CASES	SEX	AGE	LOCATION	FOLLOW-UP (FT TIME IN MONTHS)
Wang Q *et al.* 2018 (6)	1	F	54 weeks	Left parotid	Death
Irace AL *et al.* 2016 (2)	1	M	20 weeks	Left parotid	Death
Sitthichaiyakul P *et al.* 2016 (7)	1	F	54 weeks	Right parotid	24
Wang L *et al.* 2013 (8)	3	F	23 days	Right parotid	44
		M	15 weeks	Left parotid	34
		F	1 week	Right parotid	24
Farooqi KM *et al.* 2011 (9)	1	F	12 weeks	Left parotid	84
Saffari Y *et al.* 2011 (10)	1	M	At birth	Minor salivary gland	7
Saribeyoglu ET *et al.* 2010 (11)	1	M	3 days	Right parotid	48
Patil DT *et al.* 2010 (10)	1	F	At birth	Right parotid	192
Prigent M et a. 2010 (13)	1	F	At birth	Left parotid	12
Kattoor J *et al.* 2010 (14)	1	M	54 weeks	Minor salivary gland	12
Stones DK *et al.* 2009 (15)	1	M	At birth	Right parotid	Death
Marucci DD *et al.* 2009 (16)	1	F	At birth	Ectopic salivary gland	6
Mertens F *et al.* 2009 (17)	1	F	4 weeks	Left submandibular	18
Vidyadhar M *et al.* 2008 (18)	1	M	12 weeks	Right Submandibular	13
Cristofaro M *et al.* 2008 (19)	1	F	At birth	Right submandibular	12
Williams SB *et al.* 2006 (20)	5	F	10 days	Right parotid	Death
		M	1 week	Left submandibular	516
		M	8 weeks	Parotid	36
		F	24 weeks	Right submandibular	168
		M	At birth	Left parotid	NA
Ozdemir I *et al.* 2005 (21)	1	F	37 weeks	Right parotid	6
Yekeler E *et al.* 2004 (22)	1	M	At birth	Right parotid	8
Ortiz-Hidalgo C *et al.* 2001 (23)	1	M	12 weeks	Right parotid	6
Mostafapour SP *et al.* 2000 (24)	1	M	At birth	Right submandibular	12
Green RS *et al.* 2000 (25)	1	M	At birth	Right submandibular	6
Siddiqi SH *et al.* 2000 (26)	1	F	37 weeks	Right parotid	66
Garrido A *et al.* 2000 (27)	1	M	35 weeks	Right submandibular	24

REFERENCES	N CASES	SEX	AGE	LOCATION	FOLLOW-UP (FT TIME IN MONTHS)
Alvarez-Mendoza A *et al.* 1999 (28)	1	F	At birth	Right parotid	12
Seifert G *et al.* 1997 (29)	3	M	At birth	Right parotid	NA
		F	At birth	Right submandibular	NA
		M	At birth	Left parotid	NA
Hsueh C *et al.* 1992 (30)	1	F	38 weeks	Left parotid	36.5
Harris MD *et al.* 1990 (31)	1	F	40 weeks	Right submandibular	15
Casas LA *et al.* 1989 (32)	1	F	At birth	Right parotid	NA
Batsakis JG *et al.* 1988 (33)	1	M	4 weeks	Left parotid	12
Taylor GP *et al.* 1988 (34)	1	F	At birth	Parotid	6
Roth A *et al.* 1986 (35)	2	M	At birth	Left parotid	120
		M	At birth	Left parotid	108
Simpson PR *et al.* 1986 (36)	1	F	At birth	Right parotid	54
Canalis RF *et al.* 1980 (37)	1	M	At birth	Right submandibular	18
Bianchi A *et al.* 1978 (38)	3	NA	At birth	Left parotid	NA
		NA	At birth	Right submandibular	NA
		NA	At birth	Right parotid	NA
Krolls SO *et al.* 1972 (39)	1	M	1 week	Right parotid	48
Vawter GF *et al.* 1966(40)	1	M	At birth	Right parotid	36
Danziger H *et al.* 1964 (41)	1	NA	32 weeks	Right parotid	8

Abbreviations: M: Male; F: Female; FT: Free of Tumor; NA: Not Available.

vealed a voluminous formation penetrating into the left temporal fossa and ipsilateral pharyngeal lodge, characterized by clear margins and uneven signal, dislocating the pharynx. The neoformation did not infiltrate the muscle bundles, and the magnetic resonance angiography showed no alteration of the left vertebral carotid axis and vertebral bone lift.

The patient was submitted to surgery and the neoplasms was excised "en bloc". Macroscopically, the surgical sample appeared as a 200 grams oval-shaped mass measuring about 9 x 8 x 4 centimeters (**Figure 1B**). The cut section showed a solid, firm, multinodular yellowish mass. Histological examination showed a neoplastic proliferation organized in solid nests separated by loose connective tissue containing mucous material. Microcystic areas were focally present. The solid nests were composed of basaloid cells arranged in palisade near the edge of the nest. The basaloid cells became more mature from the edge of the nest to the center. Some duct structures with secretion in the lumen were sometimes observed in the nests. No tumor necrosis was found. Immunohistochemistry (IHC) was performed including the following antibodies: Anti-Pan Keratin (Ventana AE1/AE3/PCK26); anti-p63 (Ventana 4A4); anti-p53 (Ventana Bp53-11) and anti-Ki-67 (Ventana 30-9). Positive staining for Pan Keratin was observed in duct structures and non-homogeneous expression of the p63 was observed; the signal intensity appeared more intense and diffuse in the cribriform areas (80%) than in the areas with solid nests (60%) (**Figure 2A-C**). In the latter, a more intense

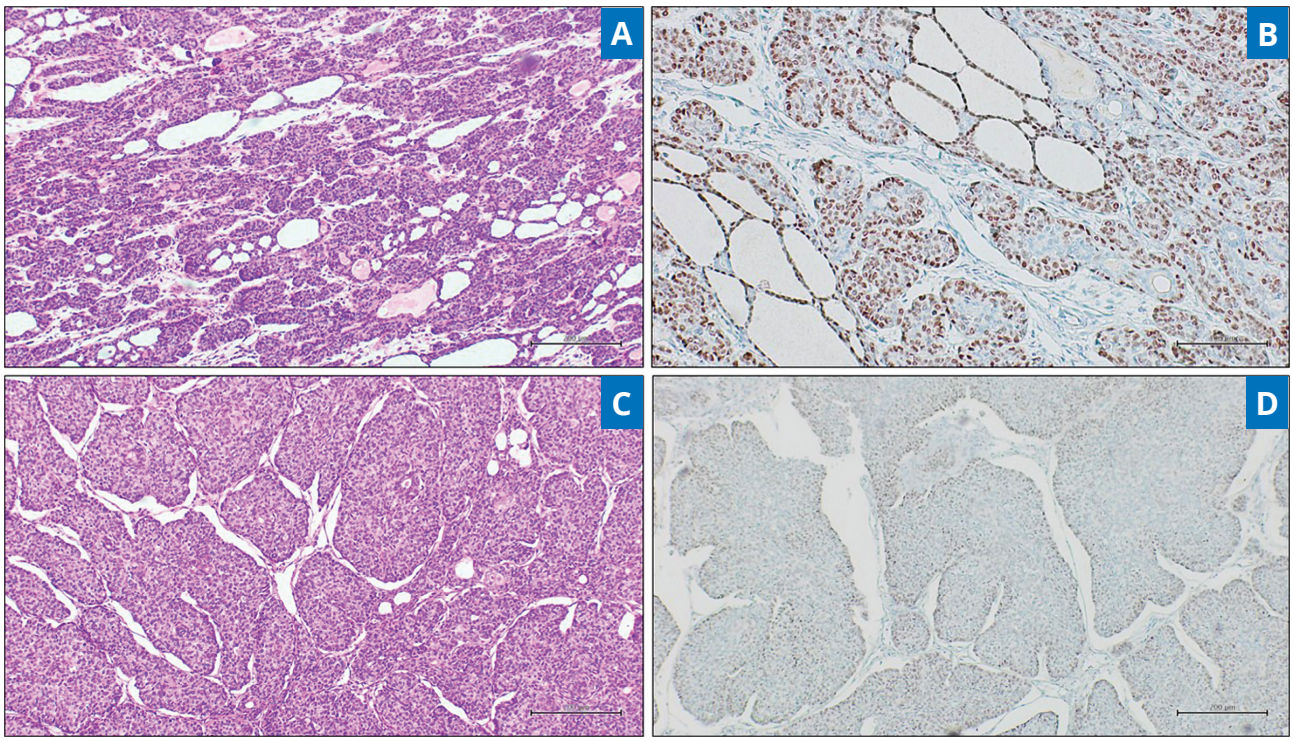

Figure 2. ***(A, B)*** *Solid organoid nests composed of primitive basaloid epithelial cells with indistinct cell borders, scant cytoplasm, large, round to oval, nuclei with high nuclear to cytoplasm ratio, are observed. In addition, ducts lined by cuboidal to columnar and image of cribriform pattern are present. p63 immunostaining showed different expression according to the architectural pattern of the neoplasm, resulting more intense and diffuse in the cribriform areas* ***(A, B)*** *than in the areas with solid nests* ***(C, D)****. (A-C: hematoxylin and eosin, original magnification 100x; B-D: p63 immunostain, original magnification 100x).*

IHC signal expression was observed at the periphery of the nests while it gradually decreased in the central cells. A homogeneous expression of Ki67 was observed in the context of the neoplasm with a positive cell population of about 20% (**Figure 3**). p53 immunostaining resulted negative. A final diagnosis of sialoblastoma was rendered. The neoplasms resulted entirely excised with disease-free surgical margins, and no other therapy was necessary. The 2 years clinical and instrumental follow-up was uneventful. Written informed consent was obtained by the parents.

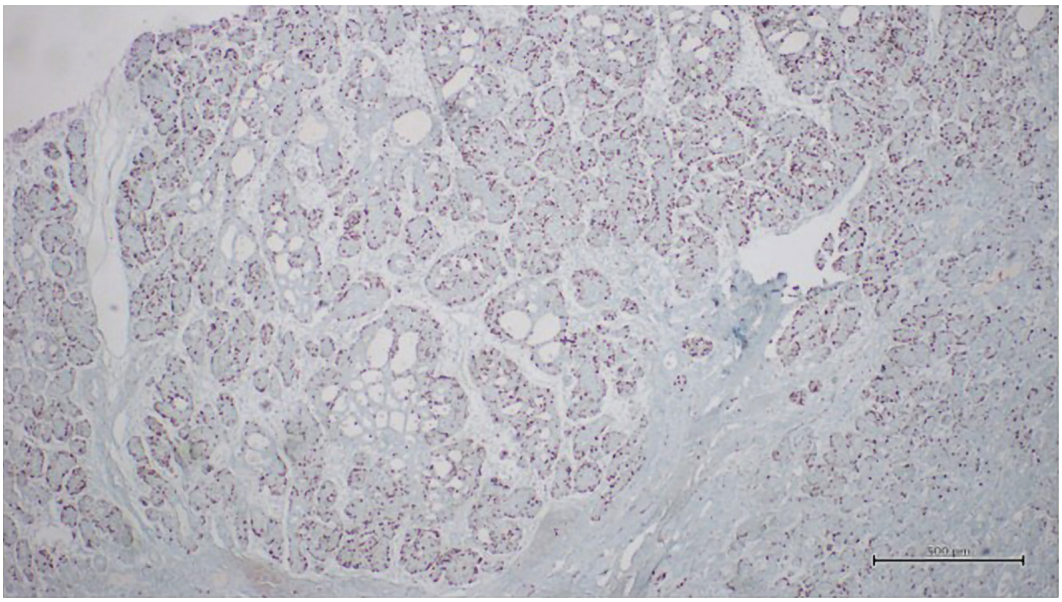

Figure 3. *Ki67 stained about 20% of the neoplastic population.*

DISCUSSION

Sialoblastoma is a very rare epithelial tumor of the salivary glands with an uncertain potential of malignancy (4). Its diagnosis may be challenging, and the differential diagnosis primarily includes other basaloid salivary gland tumors and basal cell adenoma above all. Histologically, sialoblastoma is constituted by primitive cells with basaloid features. Particularly, it is characterized by a less evident palisading arrangement of the peripheral cells, greater cytomorphological atypia and mitotic activity. Moreover, infiltration of the surrounding tissues is often present (50). The identification of some morpho-phenotypic features is essential not only for diagnostic purposes but also to predict the biological behavior of the neoplasm and therefore to lead the clinical management of the patient. Local recurrence affects about one third of patients while regional and distant metastases are seen in about 15% (2); however, death from disease is very rare (51-53) Some features have been considered to have a prognostic role such as tumor necrosis, the mitotic count and the value of the Ki-67 proliferation index, with a high Ki-67 probably associated with poor prognosis (7). More, a Ki-67 proliferative index lower than 5% has been associated with a good prognosis without disease recurrence (54). Patil DT *et al*. hypothesized that the proliferative index would not be a valid prognostic parameter, if considered individually, while the combined expression of ki67 and p53 protein would be a more useful prognostic tool predicting malignant tumor behavior (55). Our case showed a moderate and uniform Ki-67 expression of about 20%, while p53 immunohistochemical staining resulted negative.

Anyway, the association of clinical, instrumental and pathological data is essential for adequate diagnosis and management of patients. Regarding to the treatment options, the surgical resection is curative in most patients, although local recurrence, disease persistence and regional metastases are occasionally reported (7). Some Authors suggested that surgical resection with negative margins is the best therapeutic treatment (34), while chemotherapy, radiation therapy or, more recently, low-dose-rate brachytherapy should be performed only in case of recurrence or incomplete excision (56, 57). However more recent evidence suggests that such a wide surgical intervention can determine important sequelae, such as permanent damage to nerve structures, therefore other Authors recommend the execution of a neoadjuvant chemotherapy or radiotherapy treatment, also considering the excellent response to the chemotherapy (58). In conclusion, sialoblastoma is very rare neonatal tumor predominantly located in the parotid gland. It's locally aggressive and surgical treatment with negative margins is the best therapy. The accurate recognition of some morphological and immunohistochemical findings, associated with some clinical findings, is fundamental for the evaluation of its biological potential.

CONCLUSIONS

The diagnosis of sialoblastoma may be challenging and requires the comprehensive evaluation of instrumental, histological and immunohistochemical findings. The tumor is a neoplasm with uncertain potential of malignancy and some histological features, such as tumor necrosis, mitotic count and/or a high Ki-67 proliferation index may have a prognostic role. Therefore, an accurate morphological evaluation and immunohistochemical study are essential elements of the diagnostic work-up and they and might be helpful in evaluating malignant potential of the tumor.

Sialoblastoma can present recurrence and locally aggressive behavior, with regional and distant metastases. Furthermore, further molecular studies are needed to better explain the pathogenesis and the biology of this rare neoplasm.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of interests

The Authors have declared no conflict of interests.

Availability of data and materials

The data are available on request to the Corresponding Author.

Authors' contributions

All listed Authors contributed to the production of this manuscript and are listed in the appropriate order.

Ethical approval

Human studies and subjects

The study was conducted in accordance with the Declaration of Helsinki.

Animal studies

N/A.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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