Case report

Glial choristoma of the tongue. Clinicopathological analysis of a case and pathogenetic insights

Alessandro Corsi, Norman Veccia, Mara Riminucci

Department of Molecular Medicine, Sapienza University, Rome, Italy

Glial choristoma of the tongue is a rare developmental anomaly usually occurring in the first two years of life. Although diverse theories have been suggested to explain its development, they do not seem to take into account the normal tongue development. We report here on a glial choristoma of the tongue in a two-month-old male with the aim to describe the clinicopathological features of this lesion and to discuss the pathogenetic role of the cells that normally migrate from the cranial neural crests to generate the ectomesenchymal derivatives of the tongue and express neuroglial differentiation as normal developmental pathway.

Key words: glial choristoma, tongue, cranial neural crest cells, ectomesenchyme, pathogenesis.

Introduction

The term choristoma is used to indicate a cohesive tumour-like mass consisting of normal cells in an abnormal location [1]. Glial choristoma, which is a choristoma composed by glial cells either in association or not with other normal brain tissue elements, is more commonly restricted to the craniofacial region where the tongue is rarely involved [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29]. Even though different terms have been used to define the lesion, including glioma [3, 4, 16], glial/gliomatous teratoma [5, 10], heterotopic brain, or neural/glial/neuroglial tissue [6, 7, 8, 9, 11, 24, 28], the term glial choristoma is more appropriate because the lesion is a developmental anomaly and not a neoplasm and produces a tumour-like tissue mass [1, 2]. Surgical excision with free margins is curative and, because the lesion may be only suspected at clinical examination, histology and immunohistochemistry are mandatory for the definitive diagnosis [13, 15, 17, 18, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30].

The pathogenetic mechanism leading to the development of the glial choristoma in the craniofacial region is not known, and different pathogenetic theories have been suggested [1, 5, 11, 13, 16, 17, 18, 19, 21, 23, 25, 26, 27, 28, 30, 31]. Of note, a potential role of the cells normally emanating from the cranial neural crests (CNCs), which are involved in the development of the ectomesenchymal components of the human head including the tongue and express neuroglial differentiation as a normal developmental pathway [32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44], has been virtually never taken into account [1, 18, 30, 31].

We report here the clinicopathological features of a glial choristoma of the tongue in a two-month-old male and reviewed the pertinent literature. As a previously unreported finding, we observed that rare lesional cells were immunoreactive for both α-smooth muscle actin (α-SMA) and glial fibrillary acidic protein (GFAP). Based on the presence of these cells, which probably represent partially committed CNC-derived cells, we discuss the potential origin of glial choristoma of the tongue from the abnormal differentiation of orthotopically migrated CNC-derived cells toward a neural rather than ectomesenchymal derivative as normally occurs.

Material and methods

Clinical history

A well-circumscribed, firm, sub-mucosal mass was excised from the dorsum of the tongue of a two-month old boy who presented with a brief history of breathing and feeding difficulty. Available clinical data included the absence of other oral abnormalities and enlargement of neck lymph-nodes. Magnetic resonance revealed a mass, 2.5 cm in largest dimension, located on the dorsal surface of the tongue. The mass was completely excised with a margin of lingual muscular tissue. The post-operative course was referred as uneventful. At eight months post-surgery a follow-up was performed in which the patient remained free from recurrence.

Pathological analysis

The resected specimen was routinely fixed with 4% formalin and processed for paraffin embedding. Five-µm-thick sections were stained with Haematoxylin-Eosin and Sirius Red and immunostained with diverse antisera including: Glial Fibrillar Acidic Protein (GFAP, 6F2, 1 : 50; Dako, Glostrup, Denmark), S100 (1 : 1000; Dako), α-Smooth Muscle Actin (α-SMA, 1A4, 1 : 300; Dako), EMA (E29, 1 : 50, Dako), Neurofilament (NF, 2F11, 1 : 50; Dako), CD68R (PG-M1, 1 : 50, Dako) and Ki67 (Mib1, 1 : 100, DBA Italia, Segrate, Italy). Microwave oven treatment (three times for five minutes in 0.01 M sodium citrate, pH 6) was performed before immunostaining with EMA, NF, CD68R and Ki67 antisera. Double immunostaining was performed as well by means of a two-step procedure using first antiserum to α-SMA, LSAB+System-HRP kit (Dako), and 3,3'-diaminobenzidine tetrahydrochloride (Sigma, St Louis, MO, USA) as substrate and then antiserum to GFAP, FMR4-61kit (Biospa, Milan, Italy), and 5-Bromo-4-chloro-3 indolyl-phoshate/4-Nitro blue tetrazolium chloride (Roche Diagnostics GmbH, Mannheim, Germany) as substrate.

Results

Histological examination of the resected specimen (Fig. 1A) revealed a sub-mucosal mass composed of mature brain tissues (Fig. 1B, E). A fibro-vascular framework was evident and clearly highlighted by Sirius Red stain (Fig. 1C, D). Cell pleomorphism, mitosis, and necrosis were absent. Some mucosal glands were detected at the top of the lesion (Fig.1B, C) and interpreted as orthotropic normal structures. Glial cells and their fibrillary network were immunostained with GFAP (Fig. 2A) and S100 (Fig. 2B) antisera. NF immunohistochemistry identified neurons and axons (Fig. 2C). Histiocyte-like cells (microglia) were also identified based on their immunoreactivity for CD68R (Fig. 2D). The intra-lesional absence of immunoreactivity for EMA excluded the presence of meningeal-like tissue. Immunostaining for α-SMA highlighted the fibrovascular framework and rare lesional cells (Fig. 2E) were also immunostained. Interestingly, isolated α-SMA-positive cells were also immunostained with GFAP (Fig. 2F, G). The proliferation index, evaluated by Ki67 immunostaining, was low (< 1%).

Discussion

Because of its rarity, any single case of glial choristoma of the tongue can be a diagnostic clinical challenge and may offer the opportunity to discuss the pathobiological mechanisms involved in its development. From a clinical point of view, the differential diagnosis of glial choristoma of the tongue is extremely huge and includes reactive, malformative, and neoplastic lesions. No more than 30 cases have been reported since 1922, when Peterer [3] described the first case in a 6-week-old female. The age at diagnosis has been reported to range from birth [9] to 28 years [21] without significant gender difference and with a significant predominance in the first two years of life. The dorsum of the tongue is the most frequently involved site. The lesion has been described isolated in all cases except one in which cleft palate, ventricle septum defect, and patent ductus arteriosus were also present [26]. Feeding difficulty, dysphagia, and respiratory distress are the most common presenting syndrome. As in the case reported here, conservative complete surgical excision is curative. In two cases, incomplete excision was followed by local recurrence, and re-excision was curative [3, 9]. Histologically, all the lesions shared glial tissue. In some cases, other brain tissue elements, in including neurons, ependymal-like epithelium, and choroid plexus-like structures were also detected in variable combination and proportion [5, 6, 7, 8, 11, 13, 15, 17, 19, 20, 21, 25, 26]. In one case [25], meningeal-like tissue was detected as well. Thus, the case reported here fulfils the clinicopathological criteria for the diagnosis of glial choristoma of the tongue.

The pathogenetic mechanism leading to the development of the glial choristoma in the tongue is not known. No specific syndromic predisposition or aetiological factors have been identified. According to the most widely diffused theory, which has been repeatedly cited and handed down in time till to the most recently published papers [25, 26, 27, 28, 29], glial choristoma of the tongue is thought to derive from the differentiation towards neural tissue of either pluripotent embryonic remnants or displaced neuroectodermal/pluripotent cells that separate before the complete fusion of the neural tube and in-

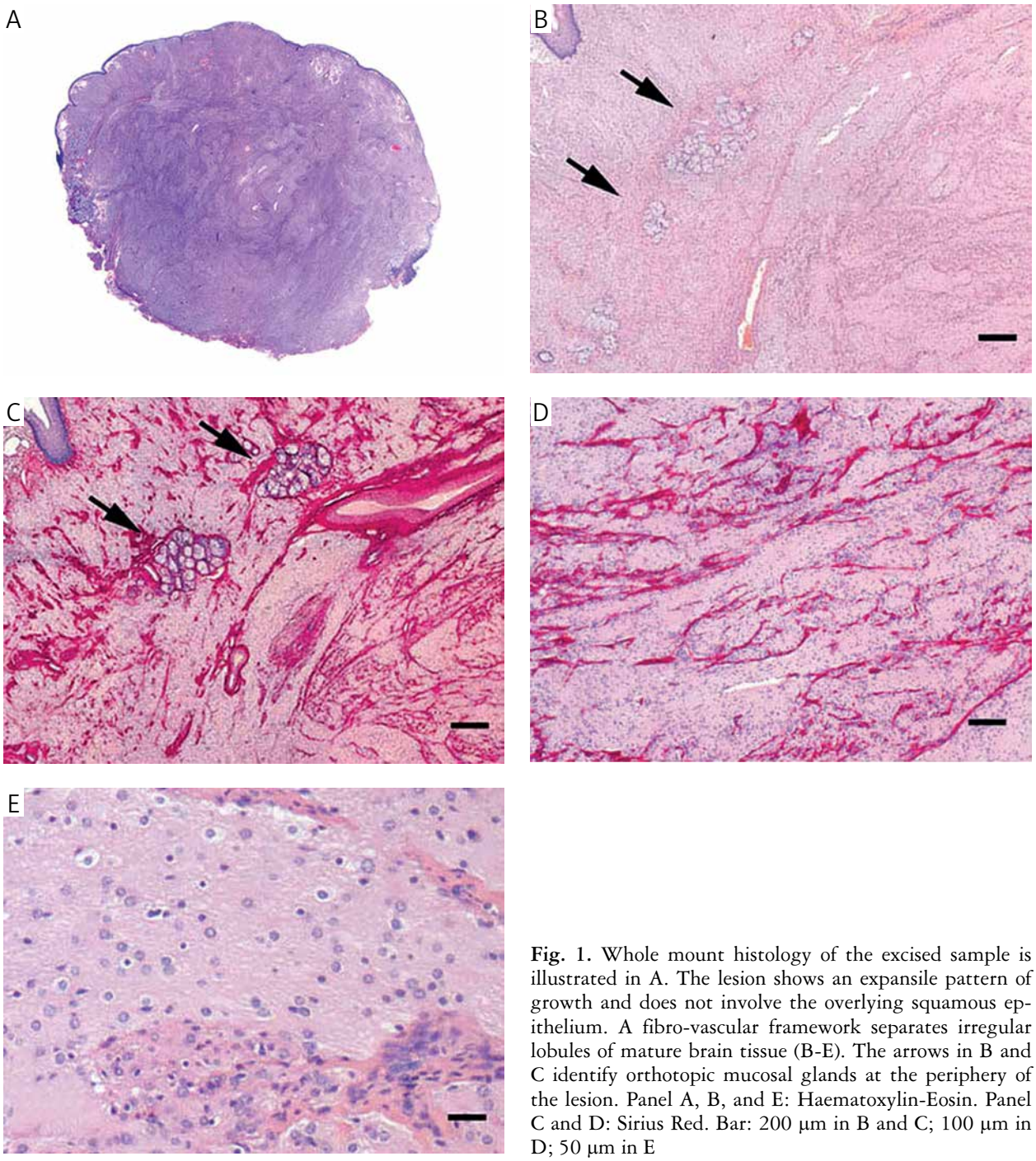

Fig. 1. Whole mount histology of the excised sample is illustrated in A. The lesion shows an expansile pattern of growth and does not involve the overlying squamous epithelium. A fibro-vascular framework separates irregular lobules of mature brain tissue (B-E). The arrows in B and C identify orthotopic mucosal glands at the periphery of the lesion. Panel A, B, and E: Haematoxylin-Eosin. Panel C and D: Sirius Red. Bar: 200 μm in B and C; 100 μm in D; 50 μm in E

tegrate with the myogenic precursors that migrate from the occipital somites to the tongue primordium, where they give rise to lingual muscle. However, these theories do not seem to take into account the normal development of the tongue and the multipotent capacity of the CNC derived cells which are primarily involved in this process. Normally, the tongue starts to develop at the end of the fourth week with the formation of multiple swellings on the floor of the pharynx, which are produced by cells that migrate from the CNC into the branchial arches, in particular the first one [32]. During and after migration, these cells contribute to the development of most of the craniofacial structures, generating, based on the effect of specific genetic and epigenetic factors and according to a hierarchical model of lineage segregation, a very wide range of ectomesenchymal and neural derivatives [33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44]. Several syndromes and congenital conditions termed neurocristopathies, which include, among others, DiGeorge syndrome, Waardenburg syndrome, and craniofacial microsomia, are well known to be related to reduced survival and improper migration of these cells [45, 46, 47]. Specifical-

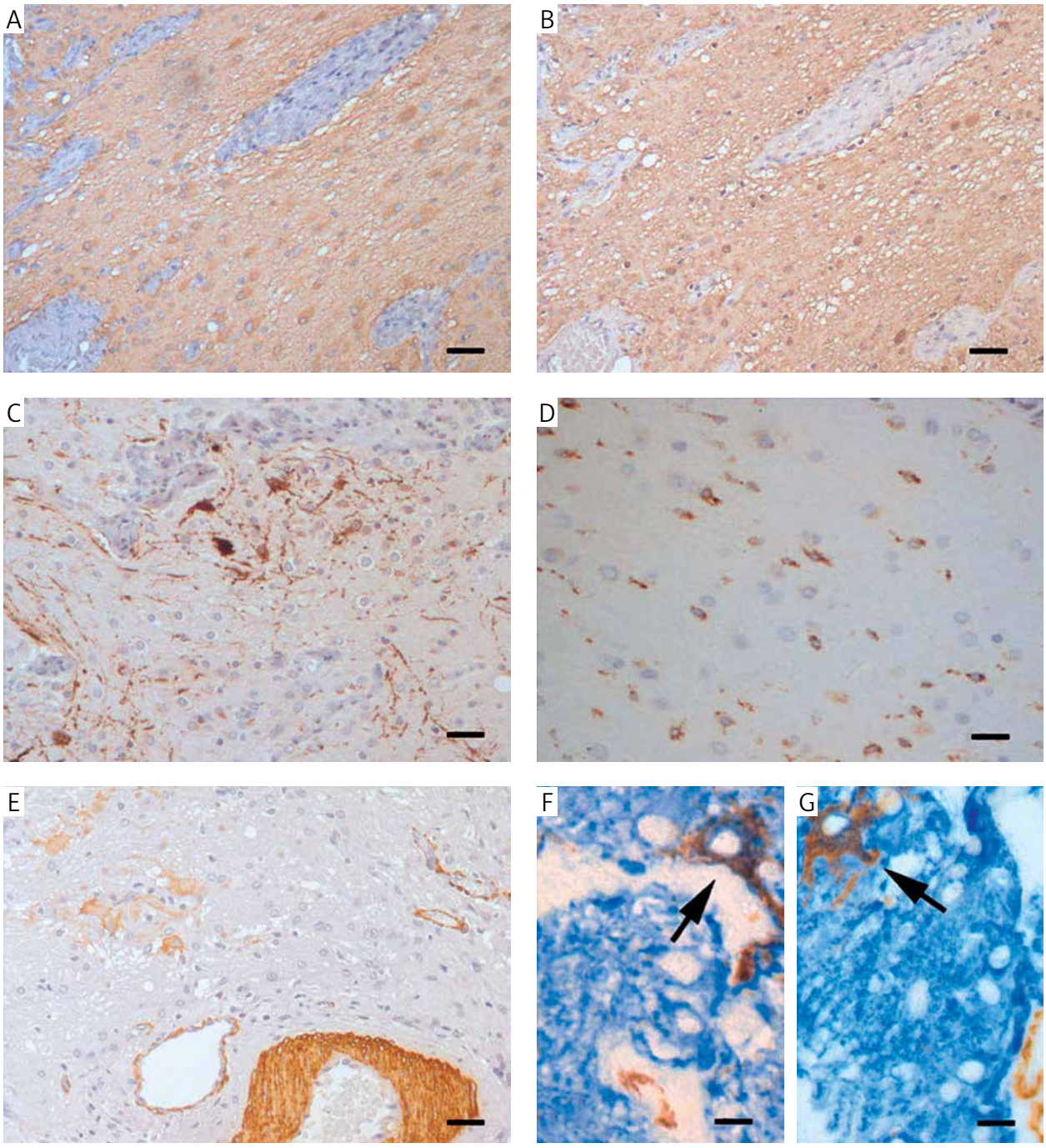

Fig. 2. Diffuse immunoreactivity of lesional cells and fibrillary network for GFAP and S100 are illustrated in A and B, respectively. Immunostains for NF and CD68R highlight neurons (C) and histiocyte-like cells (D), respectively. Rare intra-lesional cells are immunoreactive for α-SMA (E) and some of them for GFAP as well (arrows, F and G). Bar: 100 μm in A-E; 50 μm in F and G

ly, in the tongue, these cells normally provide to the generation of the ectomesenchymal cell populations (connective tissue cells, smooth muscle cells, and vasculature) that a) act as a scaffold for the myogenic progenitors migrating from the occipital somites and b) provide the molecular instruction to direct their survival, proliferation, and differentiation towards the lingual muscles [32]. Thus, based on the role of CNC-derived cells in the normal tongue organogenesis and on their multipotent differentiation capacity, glial choristoma of the tongue may be reasonably re-thought as the result of a normal, but heterotopic, differentiation toward neural derivatives of the migratory or post-migratory CNC-derived cells involved in the generation of the ectomesenchymal anlagen of the tongue. The cells co-expressing α-SMA and GFAP identified in our case may represent uncommitted CNC progenitors that, as normally occurs in vivo in the developing orthotopic brain [48], go on to differentiate heterotopically into astrocytes. Trans-

lated in the clinical scenario, it can be assumed that once the differentiation towards neural derivatives has occurred, the cell population will expand in parallel with the growth of the normal orthotopic brain, which is faster in the first two years of life, which is the age range in which glial choristoma of the tongue is more commonly diagnosed.

In conclusion, we reported here the clinicopathological features of a rare case of glial choristoma of the tongue and provide an alternative explanation of its pathogenesis according to which glial choristoma of the tongue may develop from the cells that normally emanate from the CNC and differentiate heterotopically toward neural rather than ectomesenchymal as normally occurs in the normal development of the tongue. The occurrence of glial choristoma in adulthood [21] does not contrast with our hypothesis because multipotent CNC-derived cells have been reported to persist until adulthood [40, 42, 43, 44].

The authors declare no conflict of interest.

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Address for correspondence

Alessandro Corsi
Department of Molecular Medicine, Sapienza University
Policlinico Umberto I
Viale Regina 324, 00161, Rome, Italy
tel. +39 06 4461 972
fax +39 06 4997 3376
e-mail: alessandro.corsi@uniroma1.it