Nasal Glial Heterotopia: A Clinicopathologic and Immunophenotypic Analysis of 10 Cases With a Review of the Literature

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Nasal glial heterotopia (also known as "nasal glioma"), is a rare developmental abnormality seen in a wide age group but typically presenting at birth or in early childhood. Failure to recognize the entity is the principle difficulty in diagnosis. Ten cases of nasal glial heterotopic diagnosed between 1970 and 2000 were identified. Histologic and immunohistochemical features were evaluated and patient follow-up was obtained. The patients included five females and five males with a mean age at presentation of 8.6 years (range, birth to 44 years). Most patients presented clinically with a polypoid mass in the nasal cavity, although two patients had a mass on the nasal bridge. Symptoms were present for an average of 2 to 3 months. A connection to the central nervous system was identified in one case. Masses ranged in size from 1 to 7 cm in greatest dimension (mean, 2.4 cm). Histologically, the masses were composed of astrocytes (including gemistocytic type) and neuroglial fibers intermixed with a fibrovascular connective tissue stroma. Neurons and ependymal cells were noted in two cases. Focal calcifications and inflammatory cells were identified occasionally. Masson trichrome stains the collagen intensely blue, while the neural population stains magenta. Immunohistochemical reactivity with glial fibrillary acidic protein and S-100 protein will help to confirm the histologic diagnosis, while collagen type IV and laminin can highlight the reactive fibrosis. All cases were managed by surgery. All patients were alive without complications at last follow-up (mean, 26.8 years), except for the single fetus included in the study. Nasal glial heterotopia typically involves the nasal cavity and usually presents perinatally, although three patients presented in adulthood. The subtle glial component on routine microscopy can be accentuated with a trichrome stain or by immunoreactivity with glial fibrillary acidic protein and S-100 protein. Imaging studies must be performed before surgery to exclude an encephalocele, which requires different surgery. Complete surgical excision of nasal glial heterotopias is curative.
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Index Words: Nasal glial heterotopia, nasal glioma, ectopia, immunohistochemistry, pediatrics, outcome, differential diagnosis

NASAL GLIAL heterotopia (nasal glioma) is the name used to describe a mass composed of mature brain tissue isolated from the cranial cavity or spinal canal.[1] Although the majority of these benign congenital tumors are found in the nasal region and occur on the bridge of the nose, some will be located intranasally, and the remaining few are seen elsewhere in the facial region.[2-6] Nasal glial heterotopia is frequently diagnosed in newborn infants, however, it may rarely be found in adults.

The histology of the nasal glial heterotopia is characterized by neuropil interlaced with fibrous and vascular connective tissue. Neurons and gemistocytic astrocytes may be seen in some lesions. It may be arranged in a lobular pattern, and cystic structures may be present as well.[7] The histologic picture may vary in places, and may be difficult to identify with hematoxylin-eosin stain alone; special stains and immunohistochemistry are thus of great utility when making the diagnosis.[2,8-11]

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The difference between nasal glial heterotopia and encephalocele has not yet been clarified pathologically. An encephalocele is a protrusion of brain substance connected to the rest of the brain by a pedicle with associated osseous defect: nasal glial heterotopia has no communication with the subarachnoid space or the central nervous system (CNS).[12,13] Imaging studies are required before excision to differentiate these two entities.[14] Biopsy or aspiration of these nasal masses is contraindicated because of the risk of meningitis or functional brain tissue within an encephalocele.[15]

We evaluated the clinicopathologic features of nasal glial heterotopia and compared them with nasal encephaloceles in the context of a review of the literature.

Materials and Methods

All cases diagnosed as neuroglial heterotopias and/or encephaloceles of the nasal cavity, nasopharynx, or glabella region accessioned at the Armed Forces Institute of Pathology (Washington, DC) between 1970 and 1990 in which hematoxylin-eosin–stained microscopic slide sections were available for review were evaluated. Ten cases were identified in a review of 51 cases of heterotopic CNS tissue/encephalocele of the head and neck during the same time period. Specific histologic features assessed included the types of neuroglial elements present, the presence or absence and type of associated non-neural tissues, and the presence or absence of inflammatory cells or other reactive changes.

Histologic evaluation was supplemented by a review of the clinical information submitted with each case including patient demographics, symptoms at presentation, location of the lesion, history of previous trauma or surgery, associated abnormalities or malformations, evidence of cerebrospinal fluid leakage, and radiographic or operative relationship of the lesion to adjacent CNS structures. The contributing pathologist's diagnosis was also recorded for each case.

All of the available slides, including those additionally stained with Masson trichrome, phosphotungstic acid-hematoxylin, or Nissl stains were reviewed for inclusion in the study. Immunophenotypic analysis was performed in all cases with suitable material by a standardized Envision method (Dako Cytomation, Carpinteria, CA) using 4μm-thick, formalin-fixed, paraffin-embedded sections. The analysis was performed on a single representative block for each lesion. Antibodies to glial fibrillary acidic protein (rabbit polyclonal, dilution 1:500; Dako, Carpinteria, CA), S-100 protein (rabbit polyclonal, dilution 1:800; Dako), or neurofilament protein (mouse monoclonal [clone 2F11], dilution 1:300; Dako), were examined. When required, proteolytic antigen retrieval was performed by predigestion for 3 minutes with 0.05% Protease VIII (Sigma Chemical Co, St Louis, MO) in a 0.1 mol/L phosphate buffer, pH of 7.8, at 37°C. Heat-induced epitope retrieval was performed, as required, by using formalin-fixed, paraffin-embedded tissue treated with a buffered citric acid solution pH 6.0 (Citra; Dako) and heated for 20 minutes in a steamer. Following this, the sections were allowed to cool at room temperature in a citric acid buffer solution for 45 minutes before continuing the procedure. Standard positive controls were used throughout, with serum used as the negative control.

A review of publications in English (MEDLINE 1966 to 2003) was performed, with all cases reported as "nasal glial heterotopia" or "nasal glioma" included in the review.

Results

Clinical

Lesions in five females and five males with a mean age of 8.6 years (range, birth to 44 years) were evaluated (Table 1). The females were significantly older than the male patients, with a mean age at presentation of 16.9 and 0.3, respectively. Nearly half of the patients presented with symptoms of nasal obstruction and a tumor mass. Other presenting symptoms included nasal polyps, chronic sinusitis, nasal drainage, and chronic otitis media. The masses were "external," defined as masses on the bridge or side of the nose (n = 2) or "internal," defined as tumor masses within the confines of the nasal cavity or paranasal sinuses (n = 7), with the tumor in the fetus best classified as "mixed." None of the patients had a history of prior surgery to the nasal area or reported a history of trauma. Specific information regarding the relationship of the lesions to the CNS was documented by radiographic studies and intraoperative findings. No radiographic evidence of a bony abnormality in the nasal cavity, paranasal sinuses, or base of the skull (including the cribriform plate) was documented. At the time of surgery, a cerebrospi-

Table 1. Clinical and Demographic Information

Case No.	Age*/Sex	Location	Symptom Duration*	Presenting Symptoms	CNS Relationship
1	11.0/F	Nasal cavity	n/r	Nasal polyps	n/r
2	0.5/M	Bridge of nose	0.5	Polypoid mass	No
3	0.25/M	Nasal septum	0.25	Nasal obstruction with bulge of nasal septum	No
4	0.5/M	Nasal cavity	0.5	n/r	No
5	0.04/F	Left nasal ala	0.04	Tumor mass	No
6	28.0/F	Nasal cavity	8.3	Chronic sinusitis and nasal obstruction	No
7	1.8/F	Left nasal septum	0.25	Chronic otitis media, nasal obstruction, and nasal drainage	No
8	44.0/F	Nasal cavity	0.08	Meningitis and nasal polyps	n/r
9	Birth/M	Frontal/nasal area	n/a	Fetus	No
10	0.2/M	Bridge of nose	0.2	Mass	No

Abbreviations: CNS, central nervous system; n/r, not reported; n/a, not applicable.
*Years.

nal fluid leak and/or evidence of bone erosion was noted in one patient (patient 6), while one patient (patient 8) had meningitis at the time of presentation but without documented connection. In summary, only one of the 10 patients had a documented possible CNS communication. Surgery was performed on each patient (except the fetus), with all patients alive at last follow-up without evidence of disease (mean follow-up, 26.8 years). One patient had residual disease removed 3 months afer initial presentation and has remained disease free.

Pathology

All cases were composed of varying proportions of both neurons and glia without a significant ependymal, choroid plexus, or leptomeningeal component (Figs 1, 2, and 3). The overlying epithelium (either skin, respiratory, or metaplastic squamous epithelium) was intact, although sometimes attenuated and atrophic. The glial components were often difficult to identify, especially when there was an associated inflammatory compo-

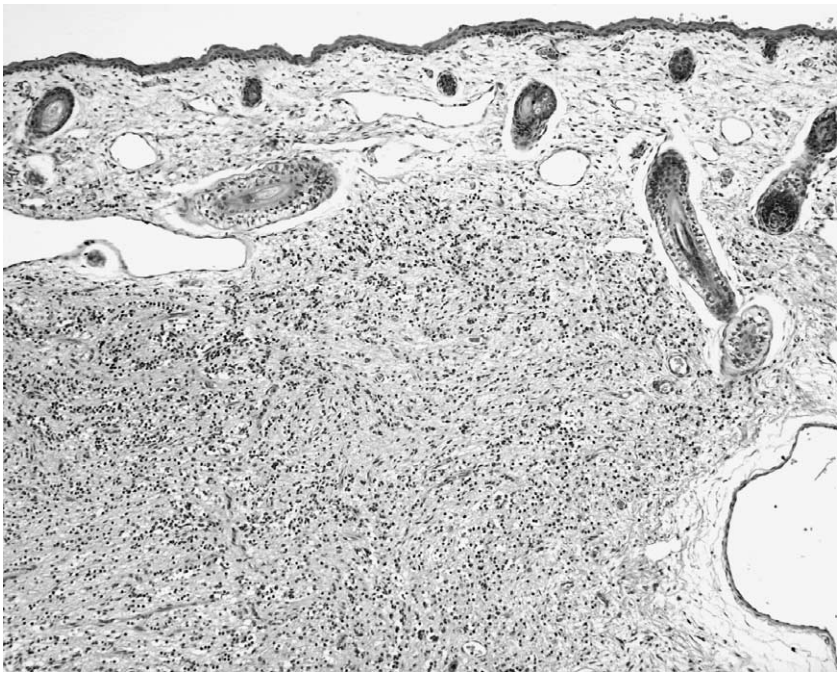

Figure 1. An intact epidermis demonstrates skin appendages subtended by reactive glial tissue composed of neuropil. Astrocytes are not seen.

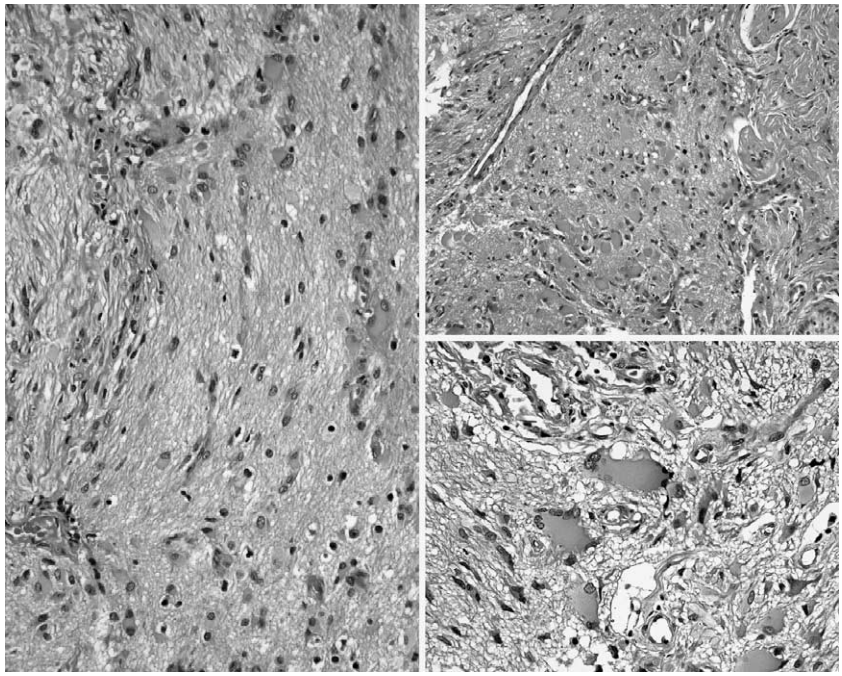

Figure 2. The left side demonstrates classic neuroglial tissue without significant fibrosis or inflammatory cells. The upper right image shows a number of "gemistocytic-type" astrocytes, while the lower right image demonstrates multinucleated "ganglion-like" cells.

nent (Fig 1) or significant fibrosis. However, gemistocytic forms and multinucleated forms (Fig 2, right) made recognition of the neural tissue easier. Chronic inflammatory cells, including lymphocytes and macrophages, and reactive gliosis (Fig 3) were present in all cases. In the cases which presented in adult patients, the degree of fibrosis or sclerosis was significantly more developed, almost completely obscuring the background glial tissue (Fig 3). The glial components were highlighted by the trichrome stain (Figs 3 and 4) and the glial fibrillary acidic protein (Fig 4) and S-100 protein immunohistochemical antibodies, when performed. Similarly, neuronal elements were Nissl stain- and neurofilament protein-positive. None of the lesions had any associated epithelial or meningeal lining nor were any of the lesions cystic. No other germ cell-derived primordia were present in the specimen, thereby excluding the possibility of a teratoma with tri-lineage differentiation.

Discussion

Nasal glial heterotopia is a rare condition, thought to be derived from either entrapped neuroectodermal tissue during the closure of the covering of the brain, or a nasal encephalocele which is covered by dura, pia, and arachnoid and later disconnected from the intracranial cavity during subsequent development.[9,12] In either event, the discrimination of nasal glioma (glial heterotopia) from encephalocele is based on the presence or absence of the connection between the mass and the intracranial tissue. However, even with high-resolution computed tomography and magnetic resonance imaging, the connection may be very small and unapparent. Furthermore, in light of the developmental abnormality, bony defects may also be seen in association with nasal gliomas while still showing no communication with the brain parenchyma.[9,14,16] The distinction may be made by the presence of meningitis and/or cerebrospinal fluid rhinorrhea either before or after surgical manipulation.[3,9,12] Curiously, the one patient (patient 8) in our series that had meningitis before diagnosis did not have a radiographic or intraoperative connection to the brain; in a second patient (patient 6), connection to the brain was seen at surgery, but no postoperative complications developed.

The medical literature characterizes nasal glial heterotopia as being a congenital mass presenting within the first year of life, with rare examples occurring later in life.[3,13,14,17] However, in this clinical series the average age at initial presentation was 8.6 years. Furthermore, the mean age at presentation for females was notably higher than for males (16.9 years v 0.3 years, respectively). The

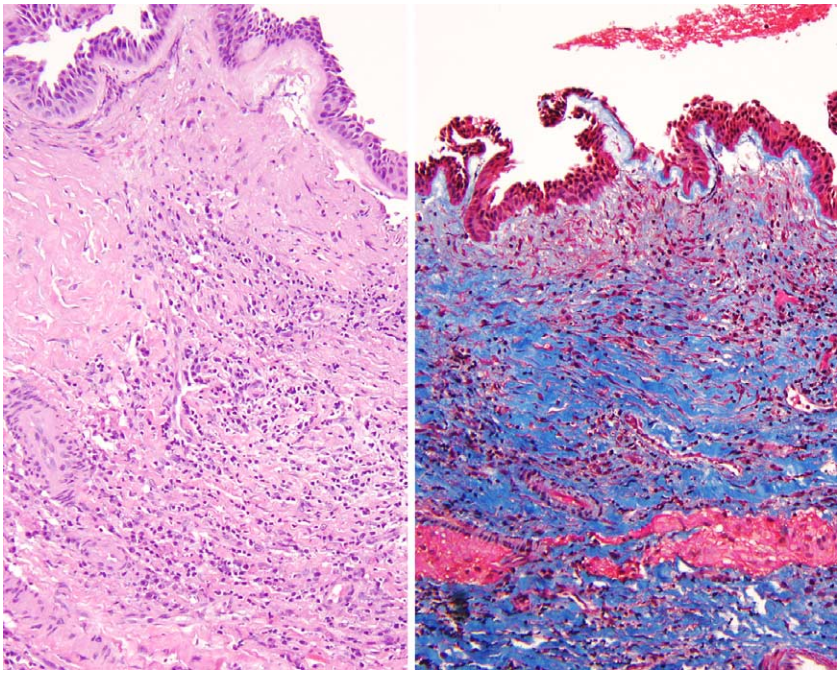

Figure 3. Extensive fibrosis below a metaplastic squamous epithelium nearly completely obscures the glial tissue (left); however, a trichrome (right) highlights the collagen (blue) and neural tissue (red).

oldest patient in our series was the only case that would be considered to have communication with the brain, perhaps suggesting a more accurate classification as an encephalocele. In this case, the notion of an acquired heterotopia rather than a developmental encephalocele is brought to light. In line with the "acquired" designation, the term nasal glial heterotopia is a more accurate description than nasal glioma, which implies a neoplasm or "tumor."

Clinically, nasal glial heterotopia may involve the external nose (approximately 60%), the nasal cav-

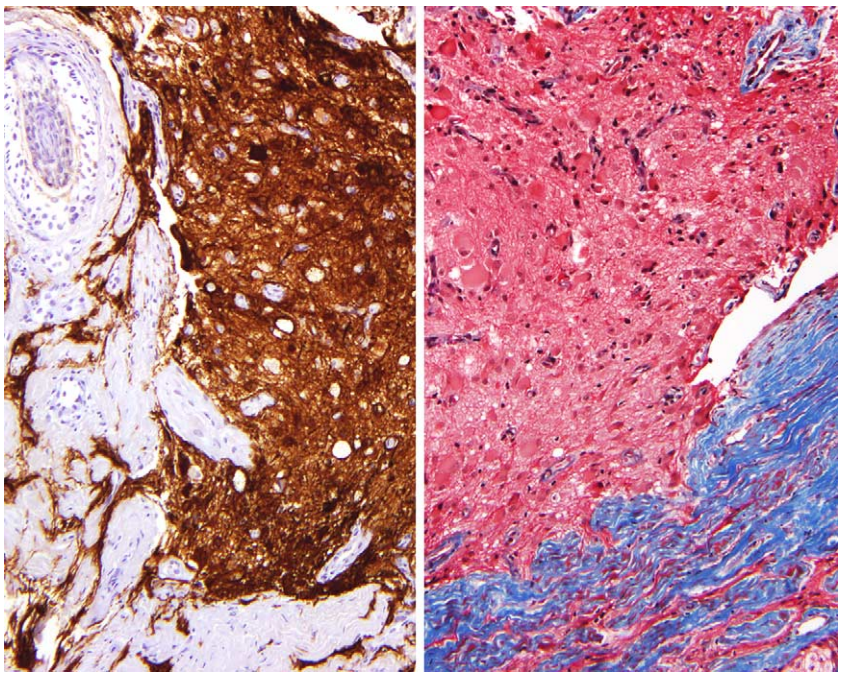

Figure 4. Trichrome stain highlights the neural tissue red (left), while the reactive background fibrosis is blue (right). A glial fibrillary acidic protein immunohistochemical study reacts with the glial tissue while there is no reaction in the surrounding reactive soft tissues.

ity (internal, 30%), or both sites (approximately 10%). Extranasal tumors manifest as a tumor mass usually on the bridge or side of the nose.[18] Hypertelorism may be present.[19] Most of these will not show any connection to the brain, further supported by the patients in this clinical series.[9] Symptoms associated with intranasal glial heterotopia are nonspecific for nasal cavity masses: nasal obstruction, polyps, allergy symptoms, and chronic otitis media.

The treatment of choice is complete surgical excision, although recurrences after surgery rarely occur. A single patient (patient 3) developed a recurrence after 3 months, with a cure achieved after additional surgery. Biopsy or fine needle aspiration of childhood nasal masses is contraindicated because of the increased risk of meningitis or perhaps the removal of functional brain material from an encephalocele.[1]

Histologically, nasal glial heterotopia and encephaloceles are characterized by varying proportions of neurons and glia, with three cases also showing gemistocytic astrocytes. There are varying degrees of fibrosis, frequently associated with inflammation (40% of cases). Calcifications and ependymal-type cystic degeneration was also occasionally seen. Mason's trichrome stain combined with S-100 protein and glial fibrillary acidic protein can be most helpful in accentuating the neural tissue in the background fibrosis. Neuron specific enolase may be used if the other stains fail. It should be noted that there are no significant histologic differences between lesions with and without demonstrable CNS connection. Therefore, the accurate diagnosis of heterotopia versus encephalocele requires knowledge of the patient's radiographic and/or operative findings.

The greatest difficulty in yielding a diagnosis of nasal glial heterotopia is not thinking of the diagnosis in the setting of an older patient with "unremarkable fibrous connective tissue." Intranasal glial heterotopia may prove quite challenging because the clinical presentation may not immediately bring this diagnosis to the forefront of the differential diagnoses. The diagnosis is considerably easier in a young child, where the clinical suspicion for extranasal glial heterotopia is high and special stains or immunohistochemistry would insure a correct diagnosis.

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