—Case Reports—

Solitary Nasal Schwannoma: Usefulness of CD34 and Calretinin Staining for Distinction from Histological Mimics

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Abstract

A solitary nasal schwannoma in a 31-year-old woman is described. The patient had a 10-year history of left nasal obstruction and presented with worsening symptoms. Computed tomography revealed a mass in the left nasal cavity extending into the ethmoidal and sphenoidal sinuses. A large, white polypoidal mass with a smooth surface was removed endoscopically piece by piece. Microscopic examination showed the tumor to be a benign spindle-cell neoplasm with predominantly mixed cellular pattern and with an indistinct focal mixture of hypercellular and hypocellular areas, likely representing Antoni A and B areas, respectively. Differential diagnoses included schwannoma, neurofibroma, solitary fibrous tumor, and meningioma. On immunohistochemical examination, the neoplastic cells showed diffuse and strong positivity for S-100. CD34 was positive primarily in the hypocellular area (Antoni B) but weak or negative in the hypercellular area (Antoni A). Staining for calretinin was focal and strong, and that for glial fibrillary acidic protein was diffuse and weak; however, stainings for estrogen receptor, epithelial membrane antigen, and α-smooth muscle actin were negative. This immunohistochemical profile confirmed the diagnosis of schwannoma. The combined use of immunostains (CD34, calretinin) could be useful for differentiating sinonasal schwannoma from its histological mimics when the typical features are weak or absent.
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Key words: sinonasal, schwannoma, neurilemmoma, CD34, calretinin

Introduction

A schwannoma (neurinoma, neurilemmoma) is a benign, slow-growing solitary tumor that can develop at any age. It is composed of Schwann cells, which are neuroectodermal cells that form a sheath around the axons to create the perineurium of the peripheral nerves[1]. Schwannomas can occur throughout the body, and approximately one-third of cases arise in the head or neck; vestibular schwannomas, often called acoustic neuromas, are among the most common tumors of the head and neck[2]. Other common sites for schwannomas include

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the mediastinum, the retroperitoneum, the intraspinal space, the paraspinal region, the sacrum, and the extremities[3,4].

Schwannomas of the nasal cavity or nasal sinuses are rare and account for approximately 4% of head and neck schwannomas[5]. Such schwannomas originate in the extracranial nerves, such as the ophthalamic and maxillary branches of the trigeminal nerve, or the autonomic nervous system, but the exact origin is often obscure[5,6]. Clinical presentations are varied and nonspecific and include nasal obstruction, epistaxis, and anosmia; facial swelling and pain are also associated with paranasal sinus involvement[7–9]. Slightly more than 100 cases have been reported in the English-language literature since the first report in 1943, and several of these reports include confirmation of the histological diagnosis with immunohistochemical staining[8,10–16].

In the present article, we describe a solitary schwannoma of the nasal cavity. Histological examination revealed a benign spindle-cell neoplasm with an indistinct mixture of hypercellular and hypocellular areas. Because these findings were atypical of schwannomas, several differential diagnoses were postulated. Immunohistochemical staining was performed to make a definitive diagnosis of schwannoma.

Case Presentation

Clinical Summary

A 31-year-old woman with a 10-year history of left nasal obstruction and headache presented to another clinic with worsening symptoms and anosmia of 3 months' duration. The family history was unremarkable. A polypoidal mass was found in the left nasal cavity. She was referred to our hospital for further examination and treatment.

Computed tomography (CT) revealed a mass with homogenous appearance in the left nasal cavity which extended posteriorly into the choana and involved the ethmoidal and sphenoidal sinuses **(Fig. 1A, B)**. No invasion into the adjacent bone tissue was evident.

The differential diagnoses based on radiographic findings favored benign tumors, such as inverted papilloma, schwannoma, and neurofibroma, but carcinoma and sarcoma could not be ruled out. Endoscopic examination revealed a soft white mass with a smooth surface filling the common nasal meatus, exerting pressure on the middle turbinate **(Fig. 1C)**, and partially extending into the ethmoidal and sphenoidal sinuses. Neither needle nor excisional biopsy was performed because we could not be certain that the biopsy specimen would represent the whole tumor. We were also concerned that the procedure might affect the morphology of the tumor and make a definitive diagnosis harder to establish. Thus, we decided to excise the lesion with surgery. However, its large size and fragility made the mass impossible to remove *en bloc*; therefore, it was removed piece by piece. The operative course was smooth and without significant hemorrhage, and the patient's condition was stable during the operation. The patient recovered uneventfully and had no postoperative complications. Although recurrence has not been found to date, the patient is being carefully followed up at our outpatient clinic.

Gross and Pathological Findings

On gross examination, the submitted sample consisted of multiple fragments of soft, white tissue measuring 3 to 13 mm in greatest dimension. Examination of cut sections showed the parenchyma to be homogenous, soft, and white without apparent necrosis or hemorrhage.

Microscopic examination revealed that the tumor was composed of compact interlacing fascicles of spindle cells, characterized by elongated and hyperchromatic nuclei **(Fig. 2A)**. No capsular formation was identified at the periphery of the lesion.

An indistinct mixture of hypercellular and hypocellular areas was observed in 85% to 90% of the tissue examined. Predominant in the remaining hypercellular areas were scattered foci of nuclear palisading, corresponding to an Antoni type A pattern **(Fig. 2B)**. The hypocelluar areas showed loosely decreased cellularity with broad, delicate collagen bundles between the tumor cells, corresponding to Antoni type B pattern. There were

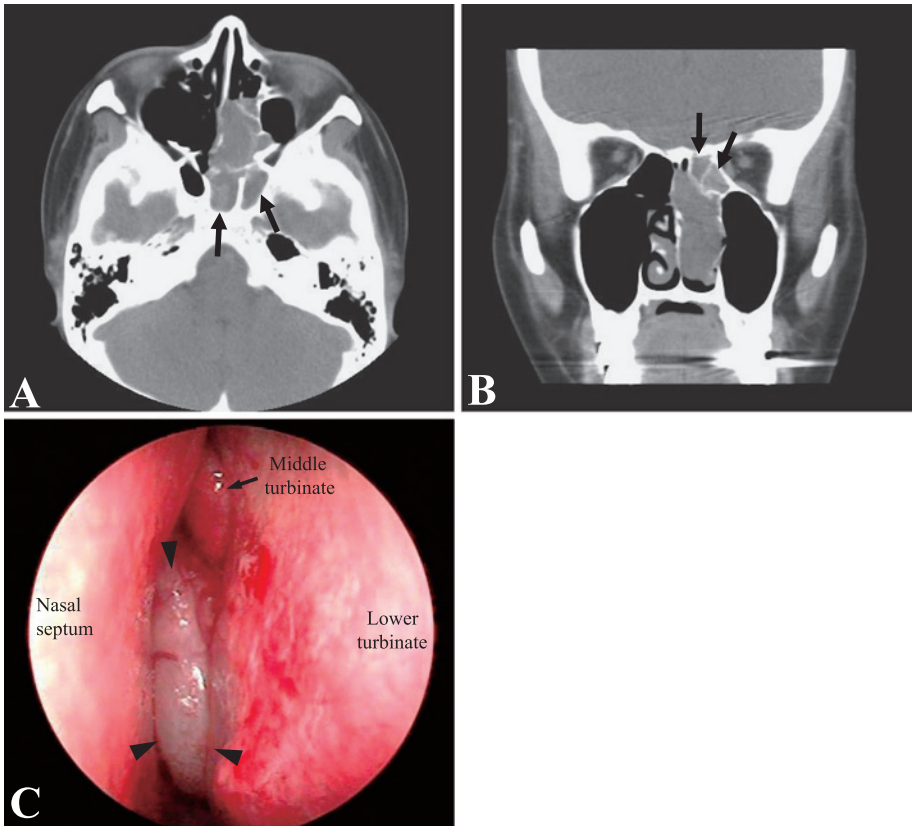

Fig. 1 Computed tomography shows a mass with homogenous appearance in the left nasal cavity extending posteriorly into the choana (A **arrows**) and involving the ethmoidal and sphenoidal sinuses (B **arrows**). No invasion into the adjacent bone tissue can be seen. Endoscopic examination revealed a soft mass (**arrowheads**) with a smooth surface filling the common nasal meatus between the nasal septum and the middle and lower turbinates (C).

also focal loose, wavy areas consisting of spindle-shaped cells and reminiscent of neurofibroma. Hyalinized blood vessels and bizarre hyperchromatic tumor cells were rarely seen. Schwannoma was suspected on the basis of the above histological findings from hematoxylin and eosin-stained sections, and immunohistochemical study was performed to confirm the diagnosis.

Immunohistochemical Findings

Immunohistochemical staining was performed of formalin-fixed, paraffin-embedded tissue. Primary antibodies included: epithelial membrane antigen (EMA), S-100, CD34, Ki67, calretinin, glial fibrillary acidic protein (GFAP), progesterone receptor (PgR), and α-smooth muscle actin (α-SMA). The tumor cells showed diffuse, strong cytoplasmic and nuclear expression of S-100 protein (**Fig. 2C**). Multifocal nuclear and cytoplasmic expression of calretinin was identified in the tumor cells (**Fig. 2D**). Cytoplasmic expression of CD34 was seen mainly in hypocellular areas but not in hypercellular areas (**Fig. 2E, F**). These findings demonstrate that the hypercellular and hypocellular areas represented Antoni A and B patterns, respectively. Diffuse, weak cytoplasmic expression of GFAP was also present. Staining for EMA, PgR, and α-SMA was negative in the tumor cells. The Ki-67 (MIB-1) labeling index was <1%.

These histological findings, along with the immunohistochemical profile, were diagnostic for schwannoma.

Discussion

The manifestations of sinonasal schwannoma are nonspecific and are usually due to tumor expansion. Symptoms can include nasal obstruction, epistaxis, and anosmia, together with facial swelling and pain

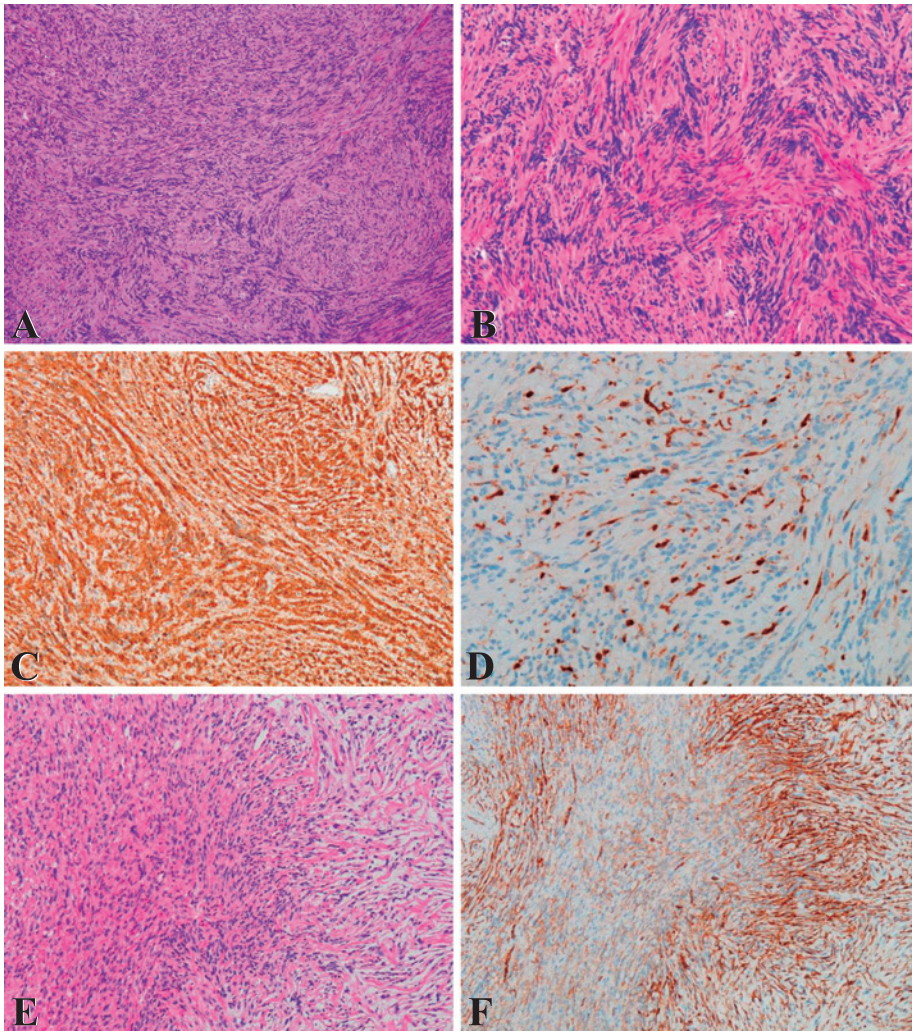

Fig. 2 The tumor was composed of compact interlacing fascicles of spindle cells, characterized by elongated and hyperchromatic nuclei with an indistinct mixture of hypercellular and hypocellular areas (×100) (A). Predominant in the hypercellular areas were scattered foci of nuclear palisading (×200) (B). The tumor cells showed diffuse, strong cytoplasmic and nuclear expression of S-100 protein (×100) (C). Multifocal nuclear and cytoplasmic expression of calretinin was identified in the tumor cells (×200) (D). Transition from the hypercellular to hypocellular areas was focally present (×200) (E). In the same region, cytoplasmic expression of CD34 was evident in the hypocellular areas but was weak or absent in the hypercellular areas (×200) (F).

associated with paranasal sinus involvement[7–9]. Solitary schwannoma has no predilection for race or sex, and the age distribution is from 6 to 78 years, with the greatest incidence in patients in their second or fourth decades[17]. Schwannomas behave in a benign fashion. They rarely recur after simple or even incomplete excision, and malignant transformation is extremely rare[18,19]. Within the sinonasal region, the ethmoidal sinus is most commonly involved, followed by the maxillary sinus[20]. In the present case, the differential diagnoses based on symptoms and radiographic findings included carcinoma, inverted papilloma, sarcoma, lymphoma, and neurofibroma. When schwannomas present with distinct histological features, microscopic identification is rarely difficult. However, diagnosis can be problematic when biopsy specimens are small or fragmented, as in our case. In such cases, immunohistochemical analysis is helpful to confirm the diagnosis.

Conventional schwannomas exhibit biphasic histologic patterns of Antoni A and B. The Antoni A

pattern is characterized by hypercellular areas with palisading of tumor cells, and the Antoni B pattern is hypocellular with no distinct pattern. Although the differentiation between the type A and B cellular patterns has no prognostic significance, pattern identification is helpful for making the correct diagnosis. In the nasal cavity and paranasal sinuses, the Antoni A pattern is predominant and comprises 64.3% of cases, the mixed cellular pattern comprises 23.7% of cases, and the Antoni B pattern comprises 12%[17]. In the present case, the histological findings were not typical of schwannoma because areas with a mixed cellular pattern were larger than areas with distinct Antoni A and B patterns. In addition, some focal areas were composed of wavy spindle-shaped cells and bundles of collagen fibers and were reminiscent of neurofibroma. Because the differential diagnoses included neurofibroma, meningioma, and solitary fibrous tumor as well as schwannoma, we felt immunohistochemical studies were necessary. Differentiating between schwannoma and neurofibroma was especially critical because the latter has greater malignant potential and is locally aggressive.

S-100 is a protein expressed by Schwann cells and is, therefore, invariably positive in all schwannomas[14]. Our finding of diffuse positivity for S-100 protein in the tumor cells strongly supported a diagnosis of schwannoma. However, the majority of neurofibromas and some types of meningioma have also been reported to be positive for S-100[21,22]. Thus, S-100 alone cannot be used to reliably differentiate schwannoma from other tumors. Calretinin is a calcium-binding protein that prevents abnormal increases in intracellular calcium levels[23]. Fine et al have shown that calretinin is positive in 96% of schwannoma cases with focal to diffuse staining but is positive in only 7% of neurofibromas with focal, weak staining[24]. The present case showed multifocal expression of calretinin in tumor cells with relatively strong staining, a pattern suggesting schwannoma. To our knowledge, the present case report is the first of schwannoma in the nasal cavity with calretinin immunoreactivity.

In the peripheral nerves, CD34 is expressed by endoneurial fibroblastic cells or dendritic cells[25,26]. In schwannomas, CD34 staining is localized within Antoni B areas but is negative in Antoni A areas[26,27]. In contrast, CD34 staining is more prominent and diffuse in neurofibromas and does not show the pattern seen in schwannomas[25]. In the present case, staining for CD34 was strong in hypocellular areas, indicative of Antoni B, but was weak or absent in hypercellular areas, indicating Antoni A. These findings are in agreement with the report of Weiss et al[26]. We assume that CD34, along with calretinin, is a marker that differentiates schwannomas from neurofibromas in histologically controversial cases. Solitary fibrous tumors sometimes appear in the nasal sinus, but the possibility in the present case was excluded by the strong staining for S-100[28,29].

The present tumor was located near the skull base, and, thus, meningioma was also a possible diagnosis. In addition, the positivity for S-100 protein in the tumor cells supported the possibility of meningioma. We stained for EMA and PgR, both of which can be markers for meningioma, and found no significant positivity[30,31]. Moreover, our case demonstrated weak immunoreactivity for GFAP, which is consistent with previous reports that GFAP can be positive in nerve sheath neoplasms, including schwannomas, although its positivity varies from focal to diffuse[32–34].

Schwannomas can originate in the peripheral motor, sensory, sympathetic, and cranial nerves[1]. In the nose and paranasal sinuses, they arise from the ophthalmic and maxillary branches of the trigeminal nerve and from the branches of the autonomic nervous system[5,6]. In fact, detecting the nerve of origin in the nasal cavity is challenging. Because the present tumor was shown with radiography to be in the posterior part of the left nasal cavity, we suspected that it had originated from the maxillary branches, specifically the posterior nasal branches, of the trigeminal nerve. Unfortunately, we were not able to confirm the origin of the tumor endoscopically.

In summary, we have documented a solitary schwannoma of the nasal cavity. Although the histological features were atypical of conventional schwannoma, the immunostaining results of diffuse S-100 expression and CD34 positivity predominantly

in the hypocellular areas supported the diagnosis of schwannoma. Staining for calretinin differentiated schwannoma from neurofibroma.

Conflict of Interest: The authors declare that no conflict of interests exists.

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