A Case of Adenoid Cystic Carcinoma Presenting as Garcin’s Syndrome without Mass Formation

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Abstract

Adenoid cystic carcinoma (ACC) is a malignant neoplasm that commonly arises in the major or minor salivary gland and usually forms mass lesions. Here, we report a case of ACC involving a 56-year-old man, who displayed right multiple cranial nerve palsies with ipsilateral severe facial pain but not any mass formation. Right submaxillary gland biopsy after repeated challenges at last revealed the primary focus of ACC with perineural invasion and without lymph node metastasis. The neurological manifestations were considered to be attributed to the perineural spread of ACC. It is extremely rare for ACC to show Garcin’s syndrome without mass formation.

Key words: adenoid cystic carcinoma, biopsy, Garcin’s syndrome, severe pain

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Introduction

As reviewed previously (1, 2), adenoid cystic carcinoma (ACC) is a malignant epithelial neoplasm, which was first described by Robin in 1853 (3) and then termed cylindroma, a synonym of ACC, by Billroth in 1856 (4). This tumor commonly arises in the major or minor salivary gland, nasopharyngeal secretory gland, or lacrimal gland, while some other rare primary sites, such as the upper respiratory tract, breast, skin, and ovary, have been reported (5). ACC is characterized by slow growth, high tendency of mass formation and local recurrence, and distant metastasis typically to the lungs, liver, and bones. It has been shown that intracranial involvement of ACC can spread via the following means: direct invasion as well as hematogenous, lymphatic and perineural invasion (5, 6).

Unilateral multiple cranial nerve palsies lacking increased intracranial pressure and other neurological deficits was first described by Seeligmann in 1896 (7), and the clinicopathological entity of these features was then established by Garcin and his colleagues in 1926 (8). In honor of their achievements, it is currently termed Garcin’s syndrome. The etiology of this syndrome has been discussed for several years, and a great variety of causative disorders have been reported. Since Guillain et al described sarcomas associated with the characteristic neurological manifestations (8), other investigators have documented several case reports focusing on the cause of Garcin’s syndrome as the following diseases: intracranial epithelial tumor (9), cylindroma (10), jugular chemodectoma (11), breast carcinoma (12), tonsillar carcinoma (13), mucinous adenocarcinoma of the nasopharynx (13), giant cell tumor of the skull base (14), colorectal carcinoma (15), and adenocarcinoma of the lung (16), as well as non-neoplastic, inflammatory disorders, triggered by infective, autoimmune, or both stimuli (17).

Here, we report a rare case of ACC characterized by the presence of Garcin’s syndrome with the lack of mass formation. We also discuss mechanisms by which the tumor resulted in its unique intracranial spread.

Case Report

A 56-year-old man was admitted to our hospital because of intractable right facial pain and ipsilateral multiple cranial nerve palsies. Ten months before admission, he noticed...
nnumbness in his right mandible, which in turn gradually deteriorated to facial pain. His previous medical history was not significant. He visited the oral surgery department in another hospital. Brain computed tomography (CT) and magnetic resonance imaging (MRI) did not show any marked alteration, whereas \(^{18}\)F-2-deoxy-2-fluoro-D-glucose (FDG)-positron emission tomography (PET)-CT scan revealed a hot spot restricted to the right soft palate. He underwent the first biopsy, at the corresponding site, and no evidence for malignancy was obtained.

Two months after onset, areas of right facial pain extended to involve those directed by the second and third branches of the ipsilateral trigeminal nerve. Seven months after onset, he developed right total ophthalmoplegia, hoarseness, dysphagia, and ipsilateral Horner’s syndrome. He was then admitted to the neurology department in the same hospital, where right multiple cranial nerve palsies were neurologically identified. Steroid pulse treatment resulted in no significant beneficial effect. For the purpose of thorough investigations, he was referred to and admitted to our hospital.

On admission, his mental status and consciousness were normal and alert, respectively, and papilloedema was undetectable in both the optic fundi. He showed right total ophthalmoplegia with blepharoesthesia, hypoalgesia in the field of all three branches of the right trigeminal nerve, peripheral type of right facial nerve palsy, positive right curtain sign, negative right gag reflex, hoarseness, dysphagia, atrophy of the right sternocleidomastoid and trapezius muscles and right half of the tongue, and right deviation of the tongue at protrusion. None of the olfactory, optic or acoustic nerve showed any deficit. He exhibited no sensory or motor paresis, alteration of deep tendon reflex, or the appearance of pathologic reflex in the extremities. Ataxia and involuntary movement were undetectable. He displayed right Horner’s syndrome but no other autonomic symptom. Taken together, the neurological manifestations of the present case were summarized as Garcin’s syndrome, involving the right third to seventh and ninth to twelfth cranial nerves and the ipsilateral cranial sympathetic nerve.

Laboratory examinations on admission revealed slight anemia (Hb 9.5 g/dL). He complained of 5 kg weight loss during 4 months so that further examinations oriented to malignant neoplasm were performed. Serum levels of tumor markers such as carcinoembryonic antigen, neuron-specific enolase, prostate-specific antigen, and squamous cell carcinoma antigen were within normal limits. Although cerebrospinal fluid (CSF) showed an elevated total protein level at a concentration of 87 mg/dL, no malignant cell was detectable by repeated CSF cytology.

Brain and spinal cord MRI and brain angiography, performed on admission, did not show any abnormality. Two months after admission, skull MRI demonstrated (i) stenosis of the pharyngeal orifice of the right auditory tube on T1-weighted image of an axial section (Fig. 1A), (ii) irregular high intensity patterns in the right parapharyngeal space on T2-weighted image of the same section (Fig. 1B), and (iii) swelling and gadolinium enhancement of the right cavernous sinus on T1-weighted image of a coronal section (Fig. 1C). The second challenge of FDG-PET-CT scan depicted a hot spot in the right soft palate and soft tissue reaching the right front of the vertebral body (Fig. 1D), to a similar extent as seen in the previous scan, and its maximum standardized uptake value (SUVmax) was 4.26, suggesting not only malignant but also inflammatory disorders. The second biopsy, at the right soft palate, gave no useful information.

His right mandibular pain gradually became uncontrollable, even with narcotic agents so that his activities of daily living were restricted, leading to a bedridden state. Although cyber-knife treatment targeting the right mandible, neck, lower face, soft palate, and parapharyngeal space was indicated, the resultant pain relief was only temporary. The third biopsy, at the right trigeminal nerve trunk, was performed, resulting in a negative finding. In spite of a simultaneous nerve cauterization, his intractable facial pain persisted.

Then, a small, firm swollen right submaxillary gland, measuring approximately 2 cm in diameter, became palpable. Neck CT with contrast materials depicted a slightly high density area surrounding the right internal carotid artery (Fig. 1E). The fourth biopsy, at the right neck soft tissue, including regions adjacent to the right internal carotid artery, as well as the submaxillary gland and the lymph nodes, was performed. Histopathological examinations of the right submaxillary gland revealed the characteristic pathological features of ACC, such as invasive proliferation of hyperchromatic atypical cells, consisting of a mixture of cytokeratin-immunoreactive glandular epithelial components and \(\alpha\)-smooth muscle actin-immunoreactive myoepithelial components (data not shown), associated with tubular and cribriform arrangements (Fig. 2A, B), stromal fibrosis, and frequent perineural invasion (Fig. 2C). Other specimens did not contain any neoplastic component. Thus, he was diagnosed as having ACC arising in the right submaxillary gland. There was no evidence of lymph node metastasis or lymphatic or hematogenous invasion (data not shown). Subsequently, the primary tumor gradually grew to appear visible in the patient’s neck.

**Discussion**

It is known that ACC can be responsible for several neurological features, including olfactory hypoesthesia (2), visual disturbance (18), neurogenic ophthalmoplegia (2, 5, 6), trigeminal neuralgia and numbness (2, 5, 6), unilateral facial, glossopharyngeal, vagal, accessory and hypoglossal nerve palsies (6), cavernous sinus syndrome (18, 19), Horner’s syndrome (6, 19-21), and pituitary dysfunction (18). In the present case, ACC manifested unilateral, markedly extensive, third to seventh and ninth to twelfth cranial nerve palsies without intracranial hypertension or long tract sign, indicative of Garcin’s syndrome. A review mentioned that the disease duration of intracranial ACC cases varies from
reported a case of ACC of the nasopharynx, readily con-

rior fossa, and invaded the dura matter. Soprani et al (21)

CT, that exhibited mass lesions which spread to the poste-

firmed by biopsy at the primary site as evidenced by skull

four cases of ACC of the submaxillary gland, readily con-

Garcin’s syndrome (5, 6, 10, 21, 24). Swash (6) reported

ing (23), as indicated in the present case. To address this issue, we should focus on

degrees of leptomeningeal involvement; some cases show a

intracranial ACC cases, it has been shown that CSF cytology

does not always detect malignant cells, reflecting the de-

Garcin’s syndrome cases ranges from two months to seven

years (6, 14-16). Thus, the total clinical course period (14

months), from onset to death, of the present case is in keep-

ing with the previous above-mentioned descriptions. In the

intracranial ACC cases, it has been shown that CSF cytology

does not always detect malignant cells, reflecting the de-

degrees of leptomeningeal involvement; some cases show a

positive finding (22), whereas others show a negative find-

ing (23), as indicated in the present case.

There has been a subset of intracranial ACC cases with

Garcin’s syndrome (5, 6, 10, 21, 24). Swash (6) reported

four cases of ACC of the submaxillary gland, readily con-

firmed by biopsy at the primary site as evidenced by skull

CT, that exhibited mass lesions which spread to the poste-

rior fossa, and invaded the dura matter. Soprani et al (21)

reported a case of ACC of the nasopharynx, readily con-

firmed by biopsy of the surrounding soft tissues evidenced

by skull MRI findings such as an expansive submucosal les-

ion of the unilateral parapharyngeal space, reaching the ad-

jacent petrous bone. By contrast, in the present case, al-

though MRI and FDG-PET-CT scan demonstrated invasive

lesions without mass formation at the right parapharyngeal

space and the unilateral cavernous sinus, three biopsies at

the corresponding regions did not yield any positive finding.

The diagnosis of ACC was finally verified by the fourth bi-

opsy at the submaxillary gland. The fact that it was very
difficult to diagnose ACC in the present case in contrast to

the previous cases may result from the lack of mass forma-

tion during the disease processes of ACC (5, 25, 26), in tu-

mor spread.

FDG-PET-CT scan has been used for detecting progres-

sive malignant tumors. Given that a hot spot on this method

Figure 1. Radiological examinations of the skull and neck ten months after onset. (A) A small arrow in an axial section of skull T1-weighted magnetic resonance imaging (T1-MRI) shows stenosis of pharyngeal orifice of the right auditory tube. (B) The dotted circle in the same section as (A) of T2-MRI indicates swelling of areas with irregular high intensity patterns in the right parapharyngeal space. (C) The large arrow in a coronal section of skull T1-MRI with contrast materials indicates swelling and gadolinium enhancement of the right cavernous sinus. (D) Arrowheads in an axial section of cranio-cervical junction level 18F-2-deoxy-2-fluoro-D-glucose-positron emission tomography surround a hot spot in the right soft palate and soft tissue adjacent to the right front of the vertebral body. (E) Large and small arrows in an axial section of neck CT with contrast materials indicate a slightly high density area and the adjacent right internal carotid artery, respectively.
clinical trigeminal neuralgia and pathological perineural involvement in inflammation, represented by edema, as well as local edema, played a pivotal role in intracranial spread. It is likely that severe intractable facial pain may be induced by trigeminal nerve involvement based on perineural invasion. A growing body of evidence indicates that trigeminal neuralgia and facial nerve palsy frequently occur in ACC cases (5, 6, 21, 25). Several studies have suggested the involvement of an inflammatory reaction in neuropathic pain and perineural invasion (28, 29). Moreover, it should be noted that perineural invasion of adnexal carcinoma has been shown to be implicated in local edema and paresthesia (30).

In the present case, it is controversial how the tumor gave rise to Garcin’s syndrome, and it is noteworthy to discuss this issue based on neuroanatomical viewpoints (31). The fact that ACC was observed within the right submaxillary gland could indicate that this lesion was the primary focus. Here it is important to emphasize that the first, second and eighth cranial nerves were preserved, and that no significant mass lesion was found on the skull base by MRI or FDG-PET-CT scan. Considering these conditions, there can be three major pathways, mediated through perineural invasion, that the tumor finally reached regions responsible for the neurological symptoms. First, ACC may involve sympathetic nerve plexus around the right internal carotid artery adjacent to the ipsilateral submaxillary gland, including the primary focus. Then, the tumor reaches the ipsilateral cavernous sinus, where it invades the parallel third to sixth cranial nerves. Second, the tumor may involve parasympathetic nerve fibers, managing salivary secretion of the submaxillary gland, through the glossopharyngeal nerve, which is intermingled with trigeminal, facial, vagal and sympathetic nerve fiber components at pterygopalatatal ganglion. This area is distal to the position where the facial nerve is separated from the acoustic nerve. This is in keeping with the evidence that ipsilateral auditory function was intact. Third, the tumor may involve the parapharyngeal space, including the ninth to twelfth cranial nerves, via the local anastomosing networks of trigeminal and sympathetic nerve branches, some of which surround the internal carotid artery. These hypotheses can explain the radiological evidence for focal lesions without mass formation in our case.

Taken together, we presented a rare case of ACC, arising in the right submaxillary gland, which was characterized by the presence of Garcin’s syndrome and the lack of mass formation. As reviewed by Alayne et al (5), the incidence of intracranial involvement has been shown to be 4.22% of the ACC cases. The negative findings in the trigeminal nerve trunk, lymph nodes, and soft part tissues of the parapharyngeal space could indicate that perineural invasion, which was barely detectable by biopsy because of the concomitant local edema, played a pivotal role in intracranial spread. It is likely that severe intractable facial pain may be induced by trigeminal nerve involvement based on perineural invasion. The present case was finally diagnosed as having ACC at the fourth biopsy. Thus, in the case of severe intractable facial pain, malignancies including ACC should be taken into consideration as a possible cause, and even if it is difficult to obtain positive findings, repeated biopsies may occasionally be useful for a definite diagnosis.

Figure 2. Histological examinations of adenoid cystic carcinoma (ACC) in the right submaxillary gland (A, B) and the surrounding soft tissue (C), obtained by biopsy. (A) Arrows and asterisks indicate the primary lesion of ACC and the surrounding non-neoplastic parenchyma, respectively. (B) The ACC lesion consists of the characteristic tubular and cribriform patterns and reactive stromal fibrosis. (C) The tumor demonstrates perineural invasion (arrows) of a peripheral nerve bundle (asterisk) adjacent to the salivary gland. Hematoxylin and Eosin staining.

reflects increased tissue glucose consumption, which may occur in malignancy and inflammation (27), it is difficult to distinguish the former from the latter. Thus, our finding of no direct pathological evidence for ACC, obtained from a hot spot in the right soft palate, identified by FDG-PET-CT scan, points to the possibility that the tissue may be involved in inflammation, represented by edema, as well as malignancy. It may be relevant to the present finding of clinical trigeminal neuralgia and pathological perineural involvement.
The authors state that they have no Conflict of Interest (COI).

References