Facial neuropathy due to axonal degeneration and microvasculitis following gamma knife surgery for vestibular schwannoma: a histological analysis

Case report

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Complete facial palsy (House–Brackmann Grade VI) developed in a 63-year-old man with a vestibular schwannoma 25 months after he had undergone two gamma knife surgeries performed 33 months apart and involving a cumulative dose of 24 Gy directed to the tumor margin at the 50% isodose line. Magnetic resonance imaging demonstrated tumor enlargement with central nonenhancement, which initially had been recognized 21 months after the second radiosurgery. Microsurgery was performed to achieve total removal of the tumor. Histological and immunohistochemical examinations of the facial nerve specimen removed from the edge of the tumor revealed a loss of axons, proliferation of Schwann cells, and microvasculitis. In this case, microvasculitis and axonal degeneration were probably the major causes of the radiation-induced facial neuropathy.

Key Words • facial paralysis • facial nerve • gamma knife surgery • radiotherapy • vestibular schwannoma

Management of a vestibular schwannoma is intended to achieve local tumor control and preservation of cranial nerve function, including hearing and facial nerve functions, to avoid social problems for patients. Recent study data have shown that GKS or stereotactic radiotherapy for small and medium tumors can provide excellent results. A reduced dose delivered to the tumor margin results in good local tumor control and excellent preservation of hearing and facial nerve functions. The rate of recurrence is approximately 5 to 8%, however, and the rate of delayed facial neuropathy is 1 to 8%. Furthermore, little is known about the mechanisms and histological characteristics of the affected facial nerves, especially in humans. In this paper we present the histological and immunohistochemical characteristics of a facial nerve that was obtained during microsurgery in a patient with complete loss of hearing and facial nerve function following two GKSs in which the cumulative radiation dose directed to the tumor margin was 24 Gy.

Case Report

History. This 63-year-old man presented with tinnitus and sensorineural hearing loss in the right ear. His facial nerve function was normal. A diagnosis of vestibular schwannoma was made based on MR imaging studies conducted at another hospital (Fig. 1 upper left). Gamma knife surgery was performed at a second institution to treat the vestibular schwannoma by using a Leksell Gamma unit (model B; Elekta Instruments, AB, Stockholm, Sweden). The tumor measured $10 \times 10 \times 10$ mm and had a volume of 0.52 cm$^3$. The procedure was planned using the KULA system (Elekta Instruments, AB), which was applied to both MR images and computerized tomography scans. Four isocenters were used to deliver a prescribed dose of 12 Gy to the 50% isodose line with the aid of an 8-mm collimator helmet (Fig. 2 left). Several months after the first GKS, the patient noted complete loss of hearing in his right ear. Magnetic resonance images exhibited a slight growth in the tumor 31 months after the initial GKS (Fig. 1 upper right). At that time the tumor measured $12 \times 15 \times 12$ mm, with a volume of 1.7 cm$^3$. The patient underwent a second GKS at the institution where he underwent the first radiosurgery. Contrast-enhanced MR images obtained 21 months after the second GKS revealed a slight increase in tumor size to $20 \times 20 \times 15$ mm and a loss of central tumor enhancement (Fig. 1 lower left). The patient began to experience right facial palsy, which deteriorated rapidly by 25 months after the second GKS. Complete facial nerve dysfunction did not improve and the tumor continued to enlarge; the patient was thus referred to our institution 27 months after the second GKS.

Examination. The patient presented with a House–Brack-
Facial neuropathy following gamma knife surgery

Fig. 1. Serial T1-weighted MR images demonstrating the appearance of the tumor over time. Upper Left: A small vestibular schwannoma is found in the right cerebellopontine angle on the patient’s original presentation. Upper Right: A slight enlargement of the tumor is noted 31 months after the initial GKS. Lower Left: A slight growth in the tumor with central nonenhancement is visualized 21 months after the second GKS. Lower Right: Again, there is a slight increase in the size of the tumor at this admission.

Operation. A lateral suboccipital retrosigmoid craniotomy was performed together with electromyographic monitoring of the cranial motor nerves. The arachnoid plane was not visible, indicating that the tumor was strongly adherent to the brainstem; the fifth, ninth, 10th, and 11th cranial nerves; and the anterior inferior cerebellar artery. Gross-total resection was achieved without injury to these structures, although more difficulty than usual was encountered. The tumor strongly adhered to the eighth cranial nerve and the facial nerve, which could not be macroscopically identified on the surface of the lesion. No electromyographic responses could be elicited from the orbicularis oris, orbicularis oculi, or nasal muscles, and thus a section of the facial nerve, extending approximately 5 mm from the RExZ, was removed along with the tumor.

Postoperative Course. The postoperative course was uneventful, but the patient’s House–Brackmann Grade VI facial palsy and complete loss of hearing remained unchanged. Postoperative MR imaging revealed total resection of the tumor. A hypoglossal–facial nerve side-to-end anastomosis was performed 3 months later. The facial palsy slightly improved to House–Brackmann Grade IV, and MR imaging revealed no evidence of tumor recurrence at the 2-year follow-up examination.

Histological Examination. Histological analysis of the portion of facial nerve obtained during surgery demonstrated axonal degeneration, demyelination, and proliferation of Schwann cells with microvasculitis (Fig. 3 upper left). At the end of the nerve that was next to the tumor, the axons had completely disappeared and were replaced by proliferated Schwann cells. At the end of the nerve that was next to the RExZ, the axons were present, but demyelination was observed. Immunohistochemical examination demonstrated a loss of axons, which was confirmed by a negative reactivity for neurofilaments (Fig. 3 upper right), and demyelination, which was supported by a negative reactivity for myelin basic protein (Fig. 3 lower left). Despite these findings, these areas displayed strong staining for the S100 protein (Fig. 3 lower right), which revealed proliferation of Schwann cells. The microvasculature in these areas demonstrated lymphocytic infiltration at the vessel walls (Fig. 4 left) and thickening of these walls with hyaline degeneration (Fig. 4 right), which are characteristic findings of vasculitis; no endothelial proliferation or thrombosis was found. Histological examination of the tumor revealed a schwannoma with extensive hemorrhage, fibrosis, and telangiectatic change. Infiltration by inflammatory cells and leakage of fibrin were also observed. Various changes had occurred in the microvasculature within the tumor, including thickening of vessel walls with hyaline degeneration and fibrin leakage as well as infiltration by foamy macrophages at the vascular walls. The presence of mitotic figures was infrequent and the MIB-1 labeling index was approximately 2%.

Discussion

Gamma knife surgery is an effective treatment for vestibular schwannomas that are smaller than 3 cm in extracanalicular diameter. A reduction in the radiation dose has been the most important factor in decreasing the complications associated with radiotherapy. An increased risk for cranial nerve complications is associated with peripheral radiation doses of 15 Gy or higher.4 A dose between 12 and 14 Gy directed to the tumor margin is now recommended and is widely used as the optimal dose for maximal tumor control and minimal complications.5,12 To date, however, the benefits and risks of repeated GKS for tumor growth after previous radiotherapy are not clear. Furthermore, the opti-
Dose Planning and Facial Neuropathy

Delayed facial neuropathy is one of the most common neurological complications after GKS for vestibular schwannoma and usually manifests approximately 6 to 28 months after radiosurgery. The incidence of delayed facial neuropathy has declined by reducing the radiation dose to the 11- to 18-Gy range; however, facial neuropathy still occurs in 1.1 to 8% of cases. The risk of developing facial neuropathy is directly correlated with a higher radiation dose to the tumor margin, and an increased risk for cranial neuropathy is associated with doses of 17.5 Gy or greater. Facial neuropathy occurred in five (33%) of 15 patients who had been treated with 25 Gy of radiation to the periphery, which is regarded as an unacceptably high risk for the development of cranial neuropathy. The patient in our study experienced complete facial palsy (House–Brackmann Grade VI) 25 months after the second GKS. In his case, the cumulative radiation dose to the tumor margin was 24 Gy, which was thought to be high enough to cause facial neuropathy.

The necessity to perform microsurgery to treat tumor enlargement after radiotherapy is estimated to be 1 to 6% of cases. Tumor enlargement is usually recognized within 3 to 6 years after radiotherapy. A reduction in the radiation dose directed to the tumor margin has not proved to decrease the incidence of tumor control during short-term follow-up reviews; however, a slight tumor enlargement with a central loss of enhancement was recognized 21 months after the second radiosurgery in the present case, despite a cumulative radiation dose of 24 Gy to the tumor margin.

More than half the cranial neuropathies that develop after radiotherapy resolve 3 to 6 months after onset. The central nervous system may be more vulnerable to radiation-induced injury if radiation is reapplied within 2 years after the initial radiation therapy. The effect of cumulative radiation doses on either the facial nerve or the interval between the initial and the second radiosurgery are not fully understood; in the present case, however, the interval between the first and second GKS (33 months) clearly was insufficient for the facial nerve to recover from the initial radiation-induced injury.

Histological Characteristics of Radiation-Induced Neuropathy

There has been little clinical experience with histological changes in peripheral nerves after GKS, although several
experimental studies have been performed. Partial axonal degeneration with focal myelin vacuolation was found in the trigeminal nerves of adult baboons 6 months after gamma knife irradiation with a maximal dose of 80 Gy, and nerve necrosis occurred after irradiation with a dose of 100 Gy. Similar histological changes were observed in the facial and cochlear nerves of rabbits: demyelination and necrotic hot spots were found after irradiation with 60 and 80 Gy; demyelination and necrosis occurred after irradiation with 100 Gy. Loss of nerve fibers stimulates the proliferation of the remaining Schwann cells to replace lost cells.17 Histological changes in smaller arterioles or in the microvasculature after irradiation consist of hyaline degeneration, fibrinoid necrosis, and adventitial fibrosis.16 Thickened vessel walls with subintimal fibrin and lymphocytic infiltration were observed in the area of brain necrosis in rats 4 months after they had undergone 75-Gy irradiation, and the same effects were found in the small arteries of rats 20 months after GKS in which the maximal radiation dose was 100 Gy.9 In the present case, the facial nerve bundle demonstrated axonal degeneration, demyelination, and proliferation of Schwann cells with microvasculitis, which could have resulted from a direct radiation-induced injury. Nevertheless, facial neuropathy developed rapidly after a slight enlargement of the tumor (only 5 mm in diameter) and a loss of central enhancement on MR images. Furthermore, the dose required to elicit these changes was much lower in this case (cumulative dose 24 Gy) than in other experimental studies (cumulative dose 60–100 Gy). Therefore, the microvasculature may have been important in the induction of the delayed damage. Axonal injury due to microvascular damage and subsequent nerve fiber loss has been considered to be a mechanism of late radiation-induced injury to sciatic nerves of dogs 2 years after intraoperative irradiation at a dose higher than 20 Gy.17 Brain necrosis in the rat following irradiation with 75 Gy may be due primarily to a microvascular effect occurring in the delayed stage.4 The axonal damage and loss are considered to result from ischemia caused by vascular damage because axons are very sensitive to hypoxia. Therefore, the facial nerve in this case may have been more vulnerable to radiation-induced injury in the presence of a microvascular disturbance due to compression by the tumor. Decreased blood flow caused by radiation-induced microvasculitis and compression by the tumor may have been the important factor that resulted in the axonal loss and demyelination of the facial nerve.

Conclusions

Axonal degeneration, demyelination, and proliferation of Schwann cells with microvasculitis were demonstrated in a facial nerve obtained during microsurgery in a patient with a vestibular schwannoma. This patient experienced complete facial palsy after he had undergone two GKSs in which a cumulative radiation dose of 24 Gy was directed to the tumor margin. Findings in this case demonstrate that central neuropathy after GKS might result from ischemia due to radiation-induced microvasculitis and compression by the tumor. Microsurgery is indicated if local tumor control is unsuccessful after an initial GKS is performed in patients with vestibular schwannomas. More clinical data and further study are needed to elucidate the pathogenesis of radiation-related cranial neuropathy to improve both the safety of radiotherapy and the selection of appropriate patients.

References


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Fig. 4. Photomicrographs demonstrating endoneural microvasculitis. Left: Lymphocytic infiltration at the vessel walls (arrow). Right: Thickening of the vessel walls with hyaline degeneration (arrow). H & E, original magnification × 400.

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