Neurofibromatosis Type 2 is a rare autosomal-dominant disorder that is characterized by the development of multiple, usually histologically benign tumors of the central and peripheral nervous system. Most commonly, the tumors include schwannomas, meningiomas, and ependymomas. The pathognomonic lesions are bilateral VSs. Compared with their unilateral, sporadic counterparts, which are approximately 20 times more common, VSs in the context of NF2 demonstrate a higher proliferation index, are more lobular, may have axons trapped within the tumor, and tend to arise earlier in life.

Both progressive bilateral VS growth and treatment of the tumors entail a risk of complete deafness and loss of all vestibular function. A common initial strategy is to undertake unilateral treatment, especially when the VSs are small, with the hope of saving hearing in the treated ear, followed by additional treatment for the contralateral tumor if hearing is indeed preserved. If hearing is lost due to the natural progression of the VS, or as a result of treatment, then typically the contralateral tumor is followed up until the tumor shows significant growth or hearing in that ear deteriorates to a non-useful level. There is relatively limited knowledge regarding the natural history of VSs in NF2.

We report on 2 patients who underwent resection of VSs, with only radiographic follow-up of their contralateral tumors. Both patients experienced marked regression of the untreated VSs; in one of the 2 cases this regression occurred in the context of recurrence of the surgically treated VS and development of a new ipsilateral lesion (facial nerve schwannoma). To our knowledge, this is the first report of such dramatic spontaneous regression of untreated VSs in NF2.

Case Reports

Case 1

Presentation, History, and Examination Findings. This 49-year-old, right-handed woman presented to the Mayo Clinic in November 2002 with a 2-year history of left ear fullness, poor hearing, intermittent headaches, and progressive gait instability. Neurological examination revealed a wide-based, unsteady gait with inability to tandem walk, hearing loss, and bilateral lateral-gaze nystagmus. An MR imaging study of the head revealed bilateral CPA tumors consistent with bilateral VS and NF2. The patient also had moderate hydrocephalus. The maximum posterior fossa diameter of the tumors was 39 mm for the left-side tumor and 27 mm for the right-side tumor, excluding the portion within the internal auditory canal. There was no family history of NF2. Magnetic
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resonance imaging of the entire neural axis did not reveal any additional tumors. An audiogram at presentation confirmed 0% speech discrimination and a pure tone average of 70 dB in the left ear and 80% speech discrimination with a pure tone average of 35 dB in the right ear.

Operation and Postoperative Course. The patient underwent placement of an external ventricular drain to treat her hydrocephalus and microsurgical removal of the larger left CPA tumor via a retrosigmoid approach. The tumor was very adherent to the facial nerve and postoperatively the patient had House-Brackmann Grade V left facial weakness. She had no ipsilateral eighth cranial nerve function postoperatively. Her nystagmus resolved by postoperative Day 3; her intracranial pressure remained normal and external ventricular drainage was discontinued. Her gait improved (compared with preoperative evaluation) and she was discharged home on Day 6.

The patient has been followed up at approximately 6-month intervals with clinical examinations, audiologic evaluation, and MR imaging to assess her facial nerve recovery and monitor her hearing status and the size of the remaining right VS. She had incomplete left facial nerve recovery to House-Brackmann Grade III by 18 months postoperatively. Four years after surgery, her audiogram continues to show 80% speech discrimination and a pure tone average of 50 dB in the right ear. She has not received any additional treatment (including surgery, radiation, chemotherapy, or alternative medical treatments) for her remaining tumor.

Untreated VS. In this case, it was possible to assess tumor size linearly and volumetrically since the patient’s presentation. Serial Gd-enhanced MR images of the brain were obtained over a postoperative period of over 4 years at regular intervals of 6–12 months. For volumetric assessment, T1-weighted Gd-enhanced tumor area in the axial plane was outlined manually and measured using QREADS, the Mayo Clinic electronic imaging software. The area of all planes was multiplied by the slice thickness of 3 mm to yield a tumor volume in cubic millimeters. After an initial increase in size of the untreated right VS, the tumor has subsequently spontaneously regressed steadily in size. The tumor has not undergone any cystic change. The volume had decreased 77%—from a maximum of 7900 mm³ to 1900 mm³—at most recent follow-up (Fig. 1). The greatest posterior fossa diameter decreased from 30.1 mm to 18.6 mm during this imaging interval (Fig. 2).

Case 2

History. This 61-year-old woman presented to another institution in 1998 with left-greater-than-right hearing loss and imbalance and was discovered to have bilateral VS and multiple spinal tumors with characteristics consistent with those of meningiomas and schwannomas. She underwent a left middle fossa craniotomy for removal of a 2-cm left VS. Hearing was not preserved but otherwise the patient did well. Imaging follow-up was performed until 2000, but then the patient was lost to follow-up.

Presentation and Examination. The patient presented to Mayo Clinic in September 2007, with a 9-month history of progressive left facial weakness. Neurological examination revealed a wide-based gait, House-Brackmann Grade VI left facial weakness, and multiple subcutaneous nodules in the upper extremities consistent with peripheral nerve schwannomas. An MR imaging study of the entire neural axis revealed a 1.6-cm right CPA tumor consistent with a VS and a 1.1-cm left CPA tumor extending through the internal auditory canal to the floor of the middle cranial fossa consistent with a left facial nerve schwannoma or combination of vestibular and facial nerve schwannomas on the left. She was also noted to have several small intracranial meningiomas and tumors in the spinal canal and spinal cord, with features consistent with schwannomas, meningiomas, and ependymomas. Her audiogram revealed no hearing in the left ear and a 60% speech discrimination score with a pure tone average of 60 dB in the right ear.

Operation and Postoperative Course. The patient underwent left translabyrinthine resection of a left facial nerve schwannoma and recurrent vestibular schwannoma, facial-hypoglossal nerve anastomosis to reanimate her paralyzed face, and placement of an auditory brainstem implant. She tolerated this very well and has not had any treatment for her right-sided tumor since or previously.

Untreated VS. An MR imaging study of the brain had been performed in 1999 at the institution where the initial surgery was performed. We were able to use film images from this study to evaluate the size of the untreated right VS and compare the measurements to those obtained from subsequent images obtained prior to surgery for the left-side tumors in 2007. We found that the untreated right VS had spontaneously regressed in greatest posterior fossa diameter from 27 mm to 16 mm over an 8-year imaging interval (Figs. 3 and 4). The volume decreased 85% from a maximum calculated volume of 12,800 mm³ to 1910 mm³.

Discussion

Regression in Sporadic VSs

The natural history of untreated sporadic VS has
been extensively studied in the past 2 decades. Many of these studies involved small cohorts (< 25 patients), followed up over a relatively limited time span, and excluded patients with NF2. Additionally, the use of various techniques to measure tumor growth—a single linear measurement of diameter versus multidimensional linear measurements versus volumetric analysis and so forth—makes interpreting the results across studies difficult.

Authors of several meta-analyses have attempted to better characterize the natural history of sporadic VSs. Selesnick and Johnson reported on the literature through June 1997, which included 571 cases of which 16 involved patients with NF2. The mean age was 64 years and mean initial tumor size was 1.18 cm. The mean growth rate was 0.18 cm/year (range 0.05–0.32 cm/year), and 46% of observed tumors showed no growth at all during a mean observation period of 3 years. There were no reports of tumor regression. Two meta-analyses, both published in 2005, reviewing > 1300 cases showed similar results. Smouha et al. reported that tumor regression was noted in 6% of 1244 cases reported in 19 studies with a mean follow-up of 3.2 years. The degree of spontaneous regression was not specified. No growth was noted in 51%. An average growth rate of 0.19 cm/year (range 0–1.0 cm/year) could be estimated from 793 patients in 13 studies. Most of the studies in this meta-analysis did not stipulate if they included NF2 patients. Similarly, Yoshimoto, reporting in the neurosurgical literature, found a tumor regression rate of 8% among 1100 patients presented in 20 studies. Once again, the degree of regression was not reported. An attempt was made to exclude patients with NF2. The annual tumor growth rate was described in 16 studies including 964 patients; the mean annual growth rate was 0.12 cm/year (range 0.04–0.29 cm/year).

Perhaps the best prospective assessment of the natural history of non-NF2–related VSs comes from Copenhagen, Denmark. Stangerup et al. have been able to follow 552 patients with serial imaging over a mean observation period of 3.6 years. There were no reports of tumor regression in strictly intracanalicular tumors, and in only 3 (0.9%) of 332 tumors that had extracanalicular extension. The degree of regression was also not reported.

Rosenberg followed up 80 non-NF2 patients over a mean of 4.4 years. Fifty-two patients had > 3 serial MR imaging scans for analysis, and 9.6% had tumor growth followed by tumor regression similar to our 2 patients. Another 7.7% had steady tumor regression. Interestingly, another 38 patients who underwent subtotal tumor removal only were followed up, and 7.9% of these patients had tumor growth followed by regression, not statistically different from the cohort that had no treatment. However, 21.1% of patients who had partial tumor removal had some degree of steady regression. Once again, the degree of tumor regression is not stated, but these are the highest reported rates of tumor regression for either subgroup.

Luetje followed 47 patients who had at least one follow-up imaging study more than a year after initial diagnosis. Six patients (12.8%) had spontaneous regression defined as a > 1 mm decrease in the maximum measurable diameter on a single image, usually in the axial plane. The median reduction in tumor size (diameter) was 6 mm (mean 7.4 mm, range 5–15 mm) over a mean follow-up period of 3.6 years. There were no reports of tumor regression in strictly intracanalicular tumors, and in only 3 (0.9%) of 332 tumors that had extracanalicular extension. The degree of regression was also not reported.
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of 3.8 years (range 1–12.5 years). The median tumor size at the time of diagnosis was 14.5 mm (mean 17.3 mm, range 10–46 mm). Notably, the largest degree of tumor regression, 15 mm reduction in maximum measurable diameter, occurred in the patient who presented with the largest tumor. None of the patients had NF2. The author hypothesized the shrinkage was due to spontaneous intratumoral vascular thrombosis and ischemic necrosis.

Regression in NF2-Associated VSs

There is only very limited information regarding the specific natural history of untreated VSs in patients with NF2. In one study of 36 VS patients including 13 with NF2, there was no statistical difference in growth rates comparing NF2 to non-NF2 VS (overall average duration of follow-up 51.3 months). Other publications with a few NF2 patients for comparison support this conclusion. No NF2 patient had tumor regression in these small series.

The most detailed available study regarding the natural history of untreated VS in NF2 involved 9 international centers contributing patients for analysis. Fifty-six patients with 84 VSs underwent follow-up MR imaging from 9 months to 2 years after the initial diagnostic image. Some degree of regression was evident in 19% of the tumors (16 of 84)—a remarkably high percentage. However, 7 of 16 regressed < 1 mm and 13 regressed < 2 mm. Most interesting, one tumor regressed almost 7 mm in short-term follow-up, similar to our cases. Twenty-one patients with 29 VS had at least 2 MR imaging studies at least 3 years apart to constitute long-term follow-up. Four tumors (14%) regressed between 1 and 2.5 mm, with no treatment. Of note, the average growth rate for short-term follow-up was 0.13 cm/year and for long-term follow-up was 0.19 cm/year, very similar to previous reports of sporadic VS.

Mautner et al. followed 37 NF2 patients with 64 VSs over a median of 3.9 years and a median of 5 serial imaging studies. Tumor size was assessed by determining the doubling time rather than with linear measurements, so there is no way to assess if any of the tumors spontaneously shrunk. The authors did find a high correlation between the growth rates of left- and right-side tumors in the same patient. Eighteen patients with NF2 who were followed up for a median of 4 years at the National Institutes of Health and had a total of 31 VSs also showed a high correlation between left- and right-side tumor growth. Only one VS showed a decrease in size during follow-up. Of note, none of the 6 NF2 patients that Massick et al. followed for a mean of 3.3 years after resection of a single VS had tumor regression of the untreated tumor. Additionally, we could not find any similar cases in the radiosurgical literature of a NF2-associated VS regressing after stereotactic radiosurgery of the contralateral tumor.

The mechanism behind such dramatic and fortunate tumor regression in our patients can only be speculated upon. We have only seen this gratifying response in 2 of the 42 NF2 patients that we are actively following up in our practice; this group of 42 includes 13 other patients who have undergone unilateral tumor removal. To the best of our knowledge, this is the first report of such significant spontaneous regression of VSs associated with NF2. It underlines the importance of careful observation of VS involving the only hearing ear in the management of bilateral VS to determine their natural growth pattern.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References
