Recurrent malignant schwannoma of the parapharyngeal space in neurofibromatosis type 1

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Abstract

Malignant schwannoma is an aggressive tumor that carries a poor prognosis despite wide excision, chemotherapy, and radiotherapy. Malignant schwannoma of the parapharyngeal space is an uncommon finding; to our knowledge, only four cases have been described in the literature during the past 30 years, and only one of them involved a patient who had clinical evidence of neurofibromatosis type 1. In this article, we describe a new case of malignant schwannoma of the parapharyngeal space in a patient who had clinical evidence of neurofibromatosis type 1. Following resection of the tumor and a total parotidectomy, the diagnosis was made on the basis of histology and immunohistochemistry. The patient underwent postoperative chemotherapy with carboplatin and UP16. However, 5 months following surgery, the tumor recurred and metastasized. The patient was then placed on a different polychemotherapeutic regimen, which was made up of 3 g/m² of ifosfamide, 1.5 mg/m² of vincristine, and 1.5 mg/m² of doxorubicin (IVA² protocol). The IVA² regimen slowed tumor growth, but 13 months after the initiation of therapy, the patient died of neoplastic cachexia. Although chemotherapy is generally ineffective in most cases of malignant schwannoma, we did experience some positive results with the IVA² protocol. Therefore, we recommend that this combination be considered as a first-line adjuvant therapy following surgery or as a first-line therapy for patients with inoperable tumors.

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Introduction

Neurofibromatosis type 1 (von Recklinghausen's disease) is a hereditary illness. Clinical symptoms include café au lait spots, sessile or pedunculated dermal tumors, and tumors of the peripheral nerves. Neurofibromatosis is known to be complicated by malignant tumors, most of which are of soft-tissue origin. The reported incidence of transformation of neurofibromas into malignant schwannomas ranges from 3 to 30%; only a small percentage of these transformations occur in the head and neck area.[1-3]

Malignant schwannoma is a highly aggressive tumor that carries a poor prognosis.[4] It requires a precise, early diagnosis based on imaging techniques and immunohistochemical studies so that an appropriate line of treatment can be determined. For low-grade tumors, the recommended treatment is surgery. For high-grade tumors, aggressive surgical resection with wide tumor-free margins supplemented by postoperative irradiation and/or chemotherapy is recommended.[4-10] Overall, chemotherapy alone is generally considered to have little effect on survival,[11-14] but its efficacy as an adjuvant treatment has yet to be clarified.

In this article, we describe the clinical history of a young man affected by neurofibromatosis type 1 whose neurofibroma of the parapharyngeal space transformed into a malignant schwannoma. Based on our experience with this case, we can suggest a new therapeutic regimen for malignant schwannoma.

Case report

In November 1996, a 25-year-old man with diffuse neurofibromatosis type 1 and multiple café au lait spots was admitted to the Department of Otolaryngology for evaluation of a painful tumor mass in the left parotid gland that had caused earache and dysphagia. On examination, the

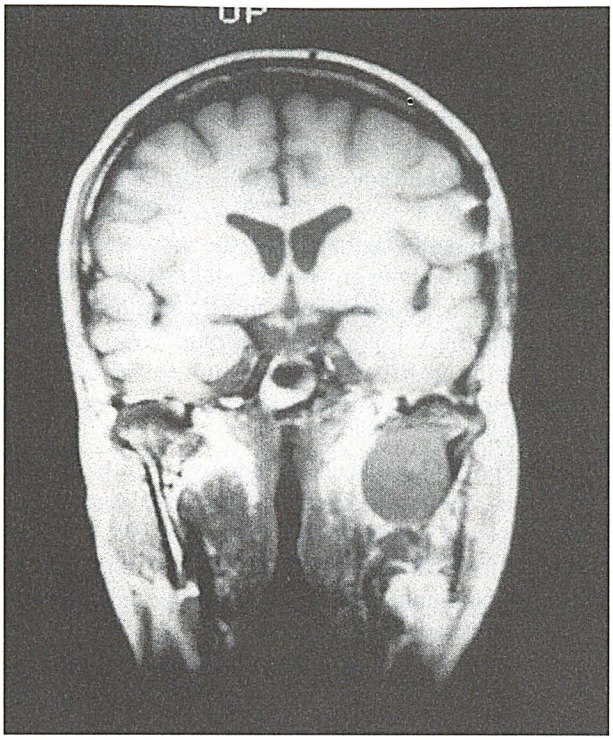

Figure 1. MRI shows the mass in the left parapharyngeal space.

tumor in the parotid area measured approximately 4 × 3 × 1.5 cm.

Magnetic resonance imaging (MRI) showed that the mass was located in the parapharyngeal space and extended into the deep lobe of the parotid gland (figure 1). A smaller mass was seen inside the left parotid. Wide resection of the tumor combined with a total left parotidectomy was carried out. The facial nerve was spared. Frozen-section examination of the tumor specimen confirmed the suspicion that it represented a neurofibroma that had transformed into a malignant schwannoma. Histologically, the tumor was made up of compact bands of polymorphous and polymetric cells with leptochromatic nuclei (figure 2). Immunohistochemical studies showed positive staining of tumor cells for vimentin and focally for S-100 protein.

Radio- and chemotherapy were not carried out because the histologic examination appeared to confirm that the tumor had been completely removed by wide-margin resection. However, 5 months later, in April 1997, the patient returned to us with a recurrence in the left parotid area. The mass had grown to 13 cm in diameter in only a few days. Enlarged exeresis of the recurrent lesion was performed, including removal of the ascending ramus of the mandible and the skin of the parotid area. The skin defect was reconstructed with a musculocutaneous flap taken from the pectoralis major and with a gauntlet (pedicle) flap taken from the temporalis.

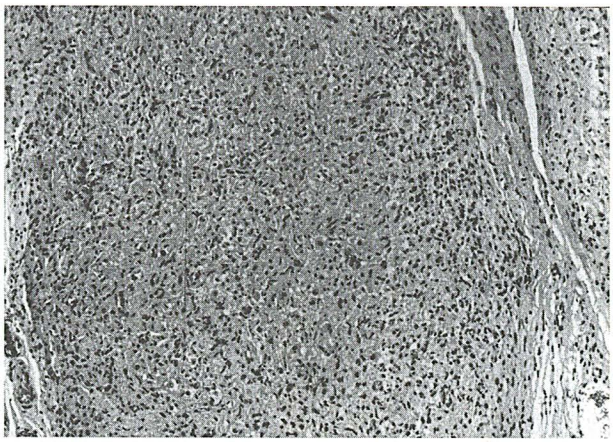

Figure 2. Histologic examination reveals an abundance of polymorphous and spindle cells (H&E, original magnification × 20).

In May 1997, chemotherapy with 500 mg/m^2 of carboplatin and 150 mg/m^2 of UP16 was administered. However, a few weeks later, the patient developed a new recurrence while undergoing chemotherapy, and the tumor rapidly grew to 20 cm in diameter. Computed tomography (CT) revealed that the tumor had invaded the left pterygopalatine fossa, the infratemporal fossa, and the skull base with infiltration of the petrous portion of the left temporal bone and the left cavernous sinus (figure 3).

Because of the size of the tumor and its continuous surface exudation, the patient did not wish to appear in public. Therefore, surgical debulking was carried out to improve the patient's remaining quality of life. In July 1997, the patient was started on 3 g/m^2 of ifosfamide, 1.5 mg/m^2 of vincristine, and 1.5 mg/m^2 of doxorubicin (IVA^2). Initially, there was evidence of a partial response to chemotherapy, and for 13 months, this antiblastic regimen appeared to slow the growth of the tumor. However, in August 1998, the patient died of neoplastic cachexia.

Discussion

Malignant schwannoma—also known as *neurogenic sarcoma*, *neurofibrosarcoma*, *malignant neurofibroma*, and recently renamed *malignant peripheral nerve sheath tumor*—is a rare form of cancer that accounts for 5% of all soft-tissue tumors and affects 0.001% of the population.[6,7] In 25 to 70% of cases, malignant schwannoma is associated with neurofibromatosis.[3,15-17] The percentage appears to be higher in patients who have a family history of neurofibromatosis.

Malignant schwannoma usually arises in the extremities, but it can affect any part of the body. In fact, cases of malignant schwannoma have been reported in the submandibular, zygomatic, and buccal areas, in the maxillary sinus, in the nasal fossa, in the esophagus, in the thoracic

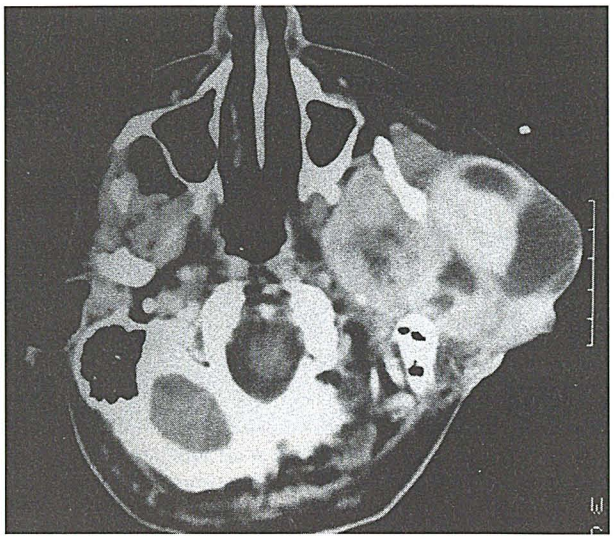

Figure 3. CT shows that the large recurrent tumor has invaded the left pterygopalatine fossa and the infratemporal fossa. Note the development outside the cheek.

vagus, in the ileal loop, in the frontoethmoid complex, and in the breast.[4,5,8,18-22] When it occurs in the head and neck area, it usually manifests as a painful, gray-white, encapsulated mass of variable size.[17]

To the best of our knowledge, only four other cases of malignant schwannoma of the parapharyngeal space have been reported in the literature during the past 30-plus years.[3,23,24] Only one of these cases involved a patient with neurofibromatosis type 1.[24]

Surgery is universally recognized as the best form of treatment.[4,6,7] Surgery should be carried out in all cases in which ample local exeresis is possible. It may be combined with a course of postop radiotherapy.[2,4,6-8,10,24-28] Radiotherapy is considered a useful palliative modality in cases in which the surrounding structures have been invaded and the tumor cannot be enucleated.[23] Radiotherapy is administered to reduce the possibility of local recurrence and to treat cases of isolated recurrence and tumors that cannot be excised. However, it is well known that malignant schwannoma is usually resistant to both radio- and chemotherapy, although chemotherapy may play a role in the treatment of surgical failures.[4,6-8,24,25,29,30] In such cases, different chemotherapeutic agents have been utilized singly or in combination. Sordillo et al[31] suggested that chemotherapy might be effective in cases of associated neurofibromatosis type 2, but the meager amount of data in the literature is frankly disheartening.[32-34] Some success has been reported, but only in isolated case reports as opposed to clinical studies. For example, Ohnishi et al described a case of malignant schwannoma of the mandibular nerve that was treated with surgery and chemotherapy; the patient had no evidence of disease at 5 years of follow-up.[27] Bruckner et al reported the complete regression of an inoperable malignant schwannoma of the posterior neck after combined-modality treatment with radio- and chemotherapy (vinblastine plus doxorubicin).[34] Athow and Kirkham observed a partial response to chemotherapy in the treatment of a malignant schwannoma of the parotid gland.[35] Most recently, Zanon et al suggested that despite the general ineffectiveness of chemotherapy, the most active drugs in the control of tumor growth in malignant schwannoma are decarbazine, doxorubicin, and ifosfamide.[21] In our patient, only IVA^2 (our second line of therapy) appeared to control the growth of the tumor. In fact, we observed clinically that the size of the tumor remained unchanged for a long period.

We acknowledge that chemotherapy has little value in most cases, but in our experience, the IVA^2 chemotherapeutic protocol yielded a good short-term result in controlling tumor growth. Therefore, we emphasize the necessity of continuing research to find an effective adjuvant therapy, and we suggest that IVA^2 be considered as a first-line choice as an adjuvant treatment following surgery or a first-line treatment for patients with an inoperable malignant schwannoma.

References

1. Allison RS, Van der Waal I, Snow GB. Parapharyngeal tumours: A review of 23 cases. Clin Otolaryngol 1989;14:199-203.
2. Senel Y, Bolulu A, Erdal F, Koybasioglu F. Malignant schwannoma located in the retroauricular region. Int J Pediatr Otorhinolaryngol 1995;33:81-7.
3. Handzic-Cuk J, Simovic S, Bumber Z. Malignant schwannoma of the sympathetic chain, combined with plexiform neurofibromas of the tongue and larynx in a patient with von Recklinghausen's disease. Eur Arch Otorhinolaryngol 1997;254:20-1.
4. Bailet JW, Abemayor E, Andrews JC, et al. Malignant nerve sheath tumors of the head and neck: A combined experience from two university hospitals. Laryngoscope 1991;101:1044-9.
5. Kautzky M, Sailer H, Franz P, Susani M. [Malignant transformation of a peripheral nerve sheath tumor in the area of the paranasal sinuses]. Laryngorhinootologie 1996;75:691-6.
6. Ducatman BS, Scheithauer BW, Piepgras DG, et al. Malignant peripheral nerve sheath tumors: A clinicopathologic study of 120 cases. Cancer 1986;57:2006-21.
7. Wanebo JE, Malik JM, VandenBerg SR, et al. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 28 cases. Cancer 1993;71:1247-53.
8. Nagayama I, Nishimura T, Furukawa M. Malignant schwannoma arising in a paranasal sinus. J Laryngol Otol 1993;107:146-8.
9. Tran LM, Mark R, Meier R, et al. Sarcomas of the head and neck. Prognostic factors and treatment strategies. Cancer 1992;70: 169-77.
10. Ducatman BS, Scheithauer BW. Malignant peripheral nerve sheath tumors with divergent differentiation. Cancer 1984;54: 1049-57.
11. Pirayesh A, Chee Y, Helliwell TR, et al. The management of retroperitoneal soft tissue sarcoma: A single institution experience with a review of the literature. Eur J Surg Oncol 2001;27: 491-7.
12. Korf BR. Malignancy in neurofibromatosis type 1. Oncologist 2000;5:477-85.

13. Mosca F, Stracqualursi A, Lipari G, et al. [Malignant schwannoma of the small intestine: A report of 2 cases]. G Chir 2000;21:149-55.
14. Drews G, Emmrich P, Hauss J, Spiegel HU. Malignant schwannoma and late-onset form of neurofibromatosis (NF-VII type) in a patient with skeletal manifestations. Langenbecks Arch Surg 1999;384:441-4.
15. Knight WA III, Murphy WK, Gottlieb JA. Neurofibromatosis associated with malignant neurofibromas. Arch Dermatol 1973; 107:747-50.
16. Riccardi VM. Von Recklinghausen neurofibromatosis. N Engl J Med 1981;305:1617-27.
17. D'Agostino AN, Soule EH, Miller RH. Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). Cancer 1963; 16:1015-27.
18. Gratz KW, Makek M, Sailer HF. Malignant melanotic schwannoma of the oral cavity. Int J Oral Maxillofac Surg 1991;20:236-8.
19. Maebeya S, Miyoshi S, Fujiwara K, et al. Malignant schwannoma of the intrathoracic vagus nerve: Report of a case. Surg Today 1993;23:1078-80.
20. Grevers G, Rocken J. Recurrent malignant schwannoma of the lower lip: Report of a case. Otolaryngol Head Neck Surg 1995; 113:138-9.
21. Zanon C, Capozzi MP, Natta F, et al. [Schwannoma of the ultimate ileal loop. Case report and review of the literature]. Minerva Chir 1994;49:211-14.
22. Malas S, Krawitz HE, Sur RK, et al. Von Recklinghausen's disease associated with a primary malignant schwannoma of the breast. J Surg Oncol 1995;59:273-5.
23. al-Otieschan AA, Saleem M, Manohar MB, et al. Malignant schwannoma of the parapharyngeal space. J Laryngol Otol 1998; 112:883-7.
24. Elias MM, Balm AJ, Peterse JL, et al. Malignant schwannoma of the parapharyngeal space in von Recklinghausen's disease: A case report and review of the literature. J Laryngol Otol 1993; 107:848-52.
25. Raney B, Schnaufer L, Ziegler M, et al. Treatment of children with neurogenic sarcoma. Cancer 1987;59:1-5.
26. Del Priore LV, Miller NR. Trigeminal schwannoma as a cause of chronic, isolated sixth nerve palsy. Am J Ophthalmol 1989;108: 726-9.
27. Ohnishi M, Tanaka Y, Tutui T, Bann S. Extensive malignant schwannoma of the mandibular nerve: Case report. Int J Oral Maxillofac Surg 1992;21:280-1.
28. Wu CM, Hwang CF, Lin CH, Su CY. Clinical records: External ear canal schwannoma: An unusual case report. J Laryngol Otol 1993;107:829-30.
29. Goldman RL, Jones SE, Heusinkveld RS. Combination chemotherapy of metastatic malignant schwannoma with vincristine, adriamycin, cyclophosphamide, and imidazole carboxamide: A case report. Cancer 1977;39:1955-8.
30. Pinedo HM, Kenis Y. Chemotherapy of advanced soft-tissue sarcomas in adults. Cancer Treat Rev 1977;4:67-86.
31. Sordillo PP, Helson L, Hajdu SI, et al. Malignant schwannoma—clinical characteristics, survival, and response to therapy. Cancer 1981;47:2503-9.
32. Hutcherson RW, Jenkins HA, Canalis RF, et al. Neurogenic sarcoma of the head and neck. Arch Otolaryngol 1979;105: 267-70.
33. Schneider M, Obringer AC, Zackai E, Meadows AT. Childhood neurofibromatosis: Risk factors for malignant disease. Cancer Genet Cytogenet 1986;21:347-54.
34. Bruckner HW, Gorbaty M, Lipsztein R, et al. Treatment of a large high-grade neurofibrosarcoma with concomitant vinblastine, doxorubicin, and radiotherapy. Mt Sinai J Med 1992;59:429-32.
35. Athow AC, Kirkham N. Malignant parotid salivary gland peripheral nerve sheath tumour in a twelve-year-old girl. J Laryngol Otol 1992;106:748-50.

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mal injury, altered blood flow, and hypercoagulable blood).[5] Hyperhomocysteinemia can cause thrombosis either directly or indirectly. For example, Lentz wrote that homocysteine can inhibit endothelial production of nitric oxide, which has antiplatelet activity and is known to prevent vasoconstriction.[6] Lentz also reported that oxidation of homocysteine can generate reactive oxygen species, such as hydrogen peroxide, superoxide anion, and hydroxyl anion. These reactive oxygen species may impair the endothelium-dependent activation of protein C, thus predisposing a patient to thrombosis. Hyperhomocysteinemia may also stimulate a proliferation of vascular smooth muscle cells.

The patient described here was treated with folic acid and a daily multivitamin that contained B supplements. Although it is not known whether thrombosis can be prevented with these supplements, she remained clot-free 15 months after the initiation of therapy.

References

1. Stahle J, Wilbrand H. The paravestibular canaliculus. Can J Otolaryngol 1974;3:262-70.
2. Mazzoni A. Vein of the vestibular aqueduct. Ann Otol Rhinol Laryngol 1979;88(Pt 1):759-67.
3. Gussen R. Vascular mechanisms in Meniere's disease. Otolaryngol Head Neck Surg 1983;91:68-71.
4. Couloigner V, Grayeli AB, Bouccara D, et al. Surgical treatment of the high jugular bulb in patients with Meniere's disease and pulsatile tinnitus. Eur Arch Otorhinolaryngol 1999;256:224-9.
5. Cohen JP, Persky MS, Reede DL. Internal jugular vein thrombosis. Laryngoscope 1985;95:1478-82.
6. Lentz SR. Mechanisms of thrombosis in hyperhomocysteinemia. Curr Opin Hematol 1998;5:343-9.