PJHRD Philippine Journal of Health Research and Development

CASE REPORT

An olfactory neuroblastoma with intracranial extension treated with chemotherapy and radiotherapy: A case report

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ABSTRACT

Background: Olfactory neuroblastoma, also known as esthesioneuroblastoma, is a rare malignant tumor that presents as a locally aggressive disease. It accounts for an incidence of 0.4 per million population affecting men and women equally in all ages. As olfactory neuroblastoma is rare, having an intracranial extension is even more unusual. Only a few cases have been reported in literature, hence, there is no widely accepted standard of care.

Case Presentation: This is a case of a 33-year-old female who presented with a 4-month history of nasal congestion which progressed to a rapidly growing nasal mass and bilateral proptosis. She soon became bedridden and exhibited signs of increased intracranial pressure. Imaging revealed a heterogeneously enhancing nasal cavity mass with intracranial extension. Biopsy and immunohistochemistry confirmed the olfactory neuroblastoma. She subsequently underwent chemotherapy and radiotherapy since the tumor was unresectable. In a span of three months, after only three cycles of chemotherapy with cisplatin and etoposide and thirty fractions of radiation therapy, the patient significantly improved from being completely bedridden to an ambulatory individual capable of self-care. We completed eight cycles of chemotherapy and referred to surgical specialists for possible resectability. However, the patient did not consent for surgery and opted to have palliative care.

Conclusion: Most cases of olfactory neuroblastoma are treated through combination therapy. The patient significantly improved from the administration of chemotherapy with cisplatin and etoposide plus radiotherapy. This case report shows the significance of chemotherapy with radiotherapy as the treatment of choice for late-stage olfactory neuroblastoma in which surgery is not amenable.

Keywords: *olfactory neuroblastoma, esthesioneuroblastoma, intracranial extension, chemotherapy, radiation therapy, case report*

Introduction

Olfactory neuroblastoma, also known as esthesioneuroblastoma, esthesioneurocytoma, esthesioneuroma, or esthesioneuropithelioma, is a rare malignant condition accounting for approximately 2% of all sinonasal tract tumors [1] which constitute less than 2% of overall malignancies and less than 3% of upper respiratory tract tumors [2]. Advanced stages occur in 25-50% of patients with olfactory neuroblastoma which involves the central nervous system for about 20-30% as the site of metastasis [3,4]. Only a few cases of olfactory neuroblastoma with intracranial extension have been reported since it was described by Berger *et al.* in 1924 [5,6]. Moreover, only a few cases were reported with intracranial extension. Locally, there were only two reported and published cases in the Philippines which were small and resectable tumors [7]. It may present in all ages with a mean age of 40-70 years old and affects men and women equally [8]. This tumor is thought to arise from the sensory neuroepithelial or neuroectodermal cells of the olfactory epithelium. The most common symptoms are unilateral nasal obstruction (70%) and epistaxis (30%) [9]. Although it involves the olfactory epithelium, it was reported that anosmia is not a common complaint (5%) [9]. Other

complaints include eye pain, visual disturbances such as diplopia, exophthalmos, unilateral proptosis, headache, and rhinorrhea.

The diagnosis of olfactory neuroblastoma is established through biopsy which presents microscopically as a small, round, blue cell tumor having lobular architecture as the most important histologic feature [1], it uses immunohistochemistry stains that is positive for synaptophysin, chromogranin, CD56, neuron-specific enolase, NFP, and S-100 protein [1]. There are three staging systems used for prognostication and guide for treatment modalities of olfactory neuroblastoma in which the most commonly used is the Kadish Staging System [10] as shown in Table 1. However, a Modified Kadish System [11] done by Morett *et al.* is more commonly used which redefines Group C as the extension beyond the nasal cavity and paranasal sinuses and Group D involves regional lymph nodes and distant metastasis. The patient is classified under Kadish Group C. In current practice, esthesioneuroblastoma is treated with surgical resection followed by radiotherapy. Generally, olfactory neuroblastoma has an excellent survival outcome with a five-year overall survival rate (OS) between 57-93% [12] that is mainly treated with current optimal therapy. Moreover, higher survival rate was observed when using neoadjuvant chemotherapy followed by surgical resection with a five-year DFR and OS of 88.9% [13].

We report a case of an olfactory neuroblastoma presented with nasal congestion which eventually progressed to a rapidly growing nasal cavity mass, and bilateral eye proptosis with signs of increased intracranial pressure treated with chemotherapy and radiotherapy. Chemotherapy with cisplatin and etoposide as the most accepted regimen in literature plus radiotherapy can significantly decrease tumor bulk [13-16]. The patient significantly improved from being completely bedridden to a gradually ambulatory individual capable of self-care. Case reports such as this will add to the developing body of knowledge and experience on this entity.

Case Report

This is a case of a 33-year-old female with no known co-morbidities who came in due to proptosis of the right eye.

Table 1. *The Kadish Staging System*

Stage	Tumor extent
A	The tumor is confined to the nasal cavity
B	The tumor involves one or more paranasal sinuses
C	The tumor extends beyond the nasal cavity and paranasal sinuses and distant metastasis

The patient complained of a four-month history of nasal congestion, numbness of the right cheek and epistaxis, associated with nasal pain, anosmia, headache, and intermittent eye pain. One month prior to consult, there was a note of right eye proptosis and nasal mass. There was no mentioned family history of malignancies or heredofamilial diseases.

Plain computed tomography (CT) scan of the paranasal sinuses revealed a large, expansile enhancing mass measuring approximately 61.4 x 42.2 x 66.10 mm (AP x W x CC) occupying the nasal cavity. The mass also showed extensions to the right middle cranial fossa and anterior cranial fossa with bony destruction of the ethmoid roof, cribriform plate, crista galli, and basisphenoid bone.

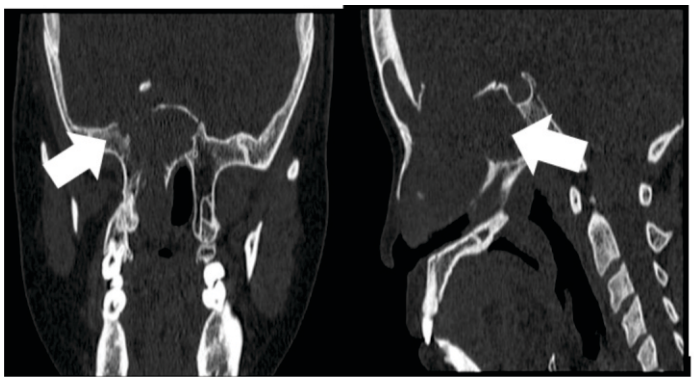

Figure 1. *Initial plain cranial computed tomography (CT) scan of the patient. A large enhancing mass occupying the nasal cavity to include the anterior and posterior ethmoid cells and extends laterally completely opacifying the right maxillary sinus with associated destruction of the bony walls of the right maxillary sinus and superiorly completely opacifying the frontal sinuses (arrow).*

On further evaluation of the tumor extent, a positron emission tomography-computed tomography (PET-CT) scan was subsidized due to the family's financial constraints. This showed an intensely fluorodeoxyglucose (FDG)-avid mass with SUV max of 26.2 centered in the nasal cavity with an increase in size and extent, involving the paranasal sinuses, orbital structures, nasopharynx, and facial bones with increased intracranial extension. There were also two metastatic nodes at level IIa, the larger of which measured 2.4 x 2.6 x4cm with an SUV max of 22.5 on the right, and one metastatic node in the right parapharyngeal region with SUV max of 10.9. The rest of the body is essentially PET negative.

Punch biopsy of the nasal mass revealed a malignant round cell neoplasm. Cytokeratin (CK), Synaptophysin, CD56, and NSE stains were positive in tumor cells and leukocyte common antigen (LCA), chromogranin and P65 stains were negative in tumor cells. Thus, an olfactory neuroblastoma was confirmed.

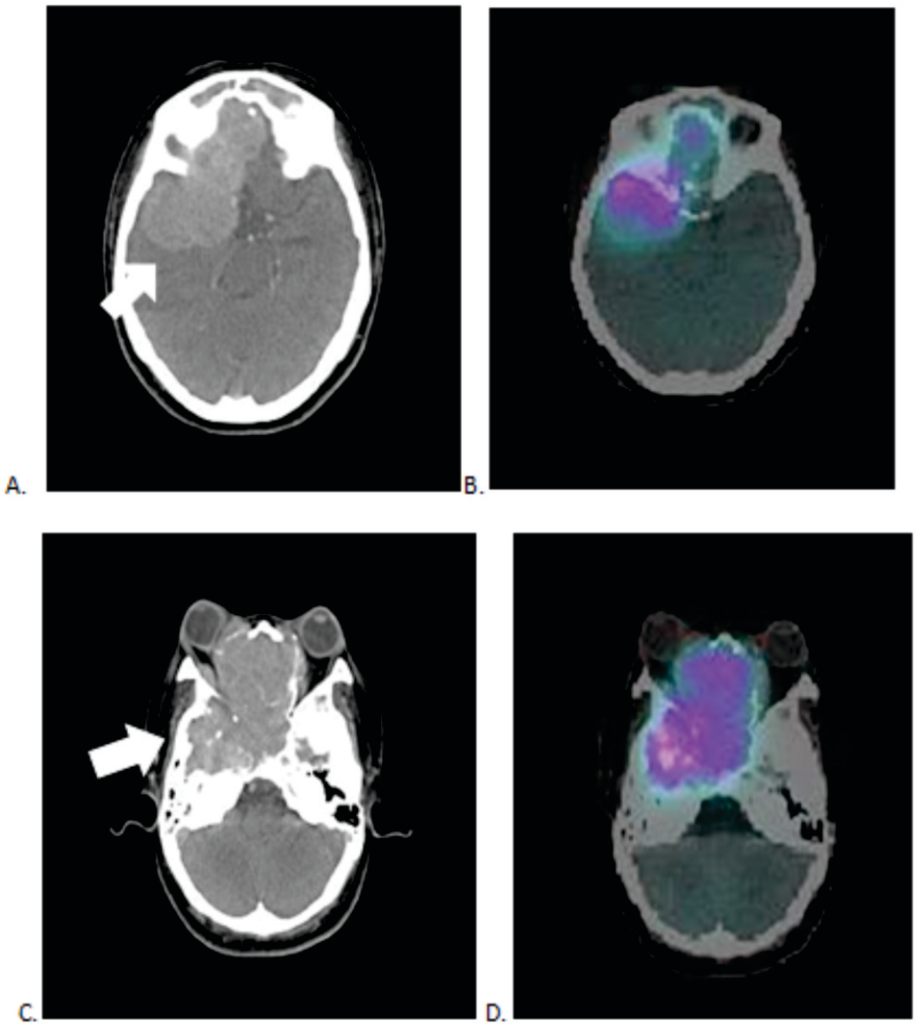

Figure 2. *Initial positron emission tomography-computed tomography (PET-CT) scan of the patient. A. Enhancing mass at the nasal cavity with intracranial extensions (arrow) to the right frontal and temporal lobes of the brain with extensive vasogenic edema in the right frontal and temporal lobes with leftward midline shift. C. Increased lateral infiltration is noted with destruction of the lamina papyracea and the left extraconal orbital component of the mass abuts and displaces the left medial rectus muscle laterally. B. and D. High metabolic activity of the mass in the nasal cavity involving the paranasal sinuses, orbital structures, nasopharynx, and facial bones with intracranial extension.*

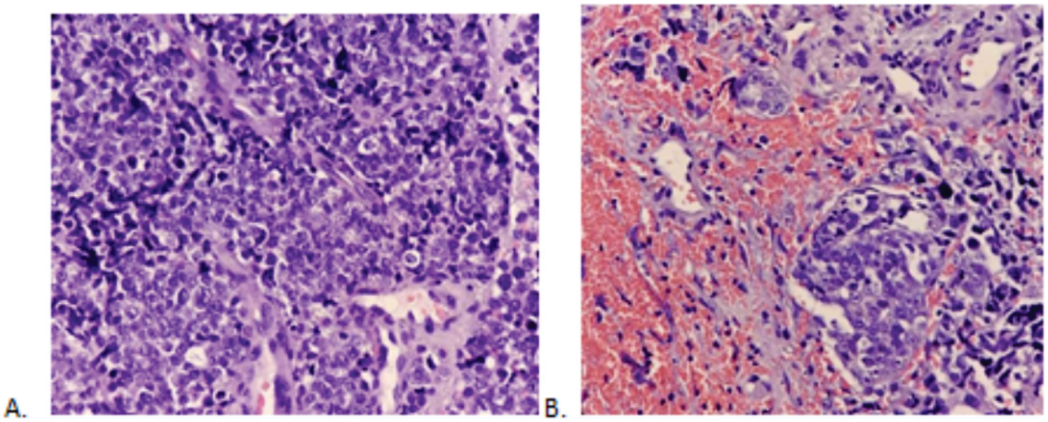

Figure 3. *Histopathologic sections of the intranasal mass. A. Section of the mass show a malignant neoplasm disposed in clusters, nests, and sheets invading the inflamed vascular stroma. The cells are medium to large, round to ovoid, hyperchromatic or vesicular nuclei with fine to coarse chromatin patterns and prominent nucleoli. B. Cytoplasm is scant to adequate and amphophilic, vacuolated, or clear. Several mitotic figures and areas of necrosis are noted.*

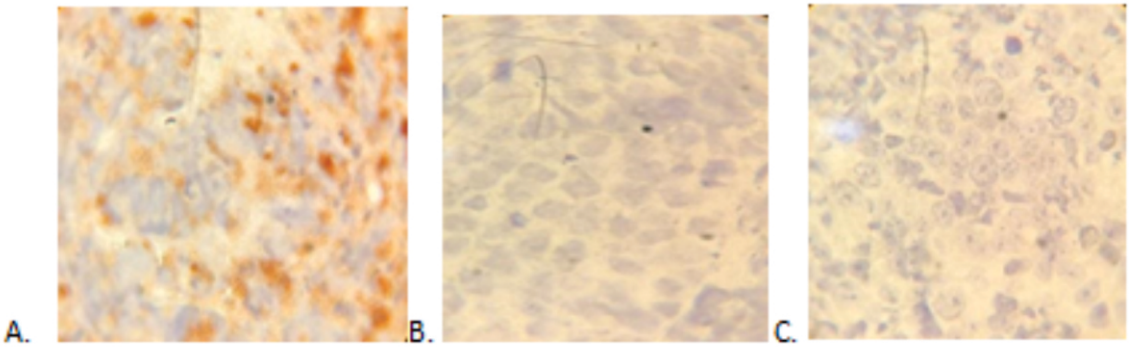

Figure 4. *Immunohistochemistry staining of the intranasal mass. A. Synaptophysin – positive in tumor cells; B. Chromogranin – negative in tumor cells; C. P65 – negative in tumor cells*

On her latest follow-up, she showed signs of increased intracranial pressure. Hence, a decision was made to immediately admit the patient for urgent medical decompression and chemotherapy. There were multiple cervical lymphadenopathies, the largest of which measures 7cm x 5cm on the right lateral aspect of the neck.

The patient then started on medical decompression using mannitol and dexamethasone to decrease the intracranial pressure. Due to the involvement of the temporal lobes on tumor extension which is the common area involved in seizures, electroencephalogram showed mild, generalized slowing of the background activity, indicative of a mild, diffuse cerebral dysfunction of non-specific etiology. During her admission, the patient underwent chemotherapy with cisplatin and etoposide at 60 mg/m2 at 20% dose reduction.

After the first cycle of chemotherapy, a marked reduction on bilateral eye proptosis and chemosis were seen as depicted in Figure 5. The patient was ambulatory with assistance, opens her left eye and able to identify objects clearly. The cervical lymphadenopathies also significantly decreased in size, although she still complained of anosmia and persistence of nasal fullness more on the right. A multidisciplinary meeting was held and a decision was made to do radiotherapy after her first cycle of chemotherapy.

She underwent Intensive Modulated Radiotherapy 6 MV with a daily dose of 200 cGy for 30 fractions having a total dose of 6,000 cGy. After 30 fractions of radiotherapy, she had decreased nasal fullness described as being able to breathe on the right nasal cavity and was starting to smell coffee and alcohol. Furthermore, extraocular muscles were now intact on both eyes, the right showed minimal eye opening with light perception, shallow nasolabial fold on the right, and motor weakness of the right upper and left lower extremity upon strength testing. A 3x3 cm cervical lymphadenopathy on the right lateral aspect of the neck was noted. On the second cycle of chemotherapy with cisplatin and etoposide, the dose was increased to 100% which she tolerated well.

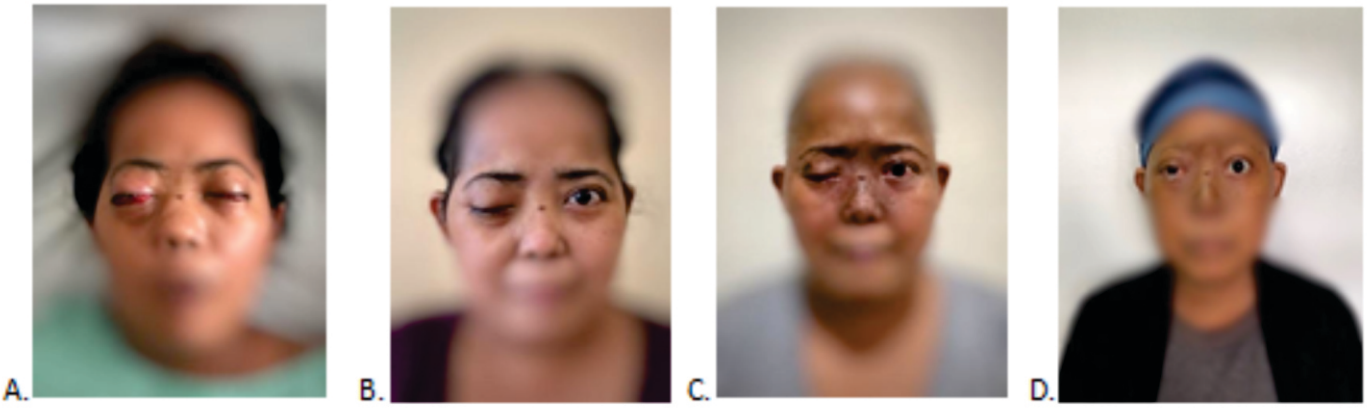

Figure 5. *Course of Therapy. A. Initial presentation on her latest follow-up exhibiting bilateral eye proptosis, crusting, and matting of lashes, with evident diffused hemorrhagic chemosis, septal deviation to the left. B. After 1st cycle of chemotherapy with marked reduction on bilateral eye proptosis and chemosis. C. After 30 sessions of radiotherapy, moon facies was seen with right eye showing minimal eye opening and hair loss. Hyperpigmentation on nasal area due to radiotherapy. D. After completion of eighth cycle of chemotherapy, the patient had significant weight loss and the right eye remained with spontaneous opening without proptosis but with watery discharge.*

The patient underwent third cycle of chemotherapy which she again tolerated well. At this point, she was able to open her right eye. However, the right eye was only able to have light perception and cannot open autonomously without the left eye being opened simultaneously. She was also able to ambulate independently and no other toxicities were reported.

Chemotherapy was completed for 8 cycles with minor toxicities reported such as persistent vomiting and generalized body weakness which may still be attributed to the medications used. During the remaining cycles of chemotherapy, we had to delay a week prior to the next cycle due to previously mentioned toxicities which were medically managed accordingly.

After completing 8 cycles, the patient persistently showed marked improvement to which she was able to independently perform activities of daily living. There was resolution of the right eye proptosis. There was evident improvement in her visual acuity on both eyes as she was able to count fingers, as compared from the time of initial presentation with only light perception.

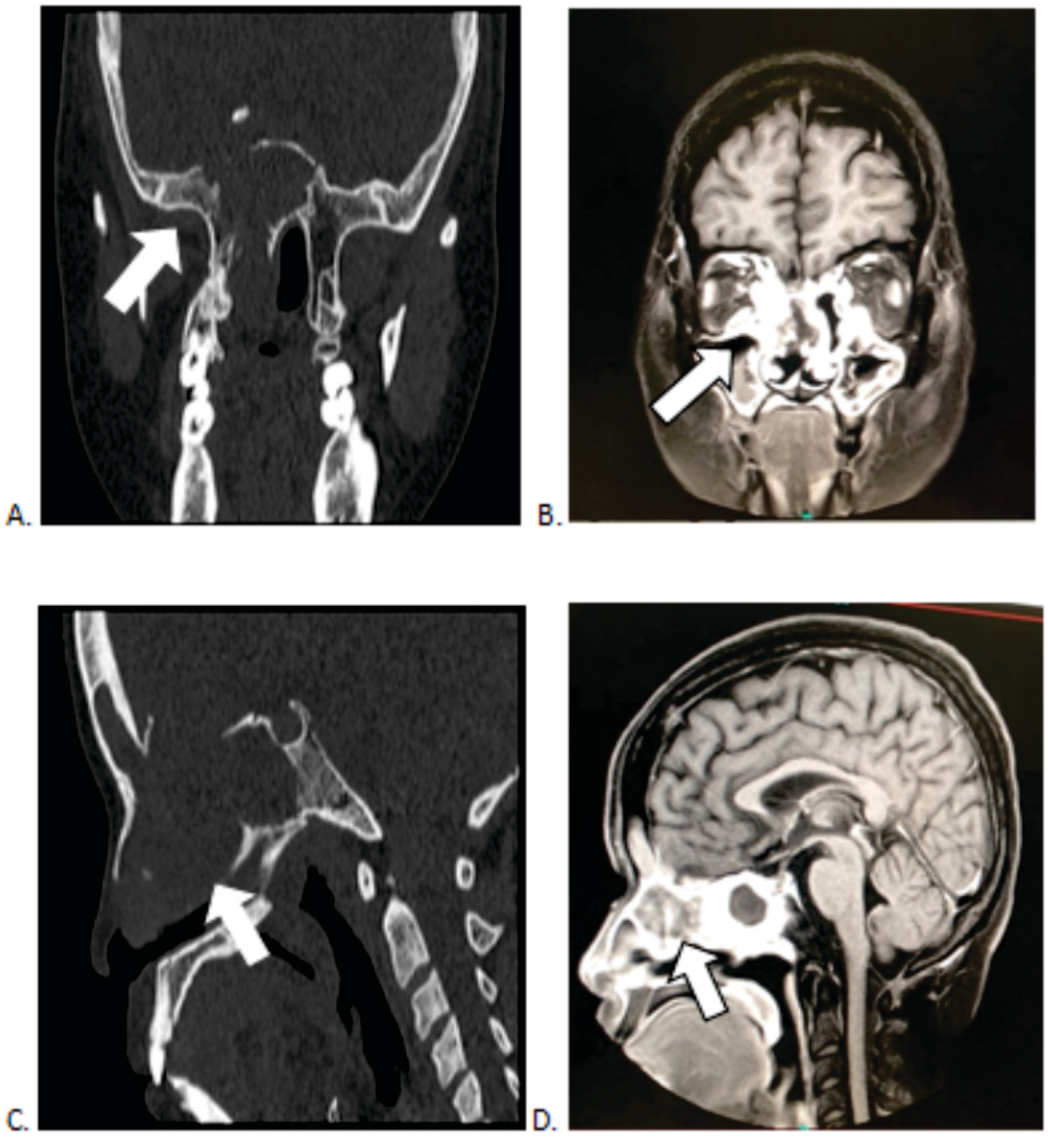

Figure 8. A comparison of the previously seen mass using cranial magnetic resonance imaging with intravenous contrast. A and C shows the previously seen large enhancing mass occupying the nasal cavity and paranasal sinuses. B. An interval decrease in the size of the previously seen lobulated, heterogeneously enhancing, expansile mass occupying the nasal cavity, more on the right, approximately measuring 57.3 x 34.1 x 39.9 mm (AP x T x CC; previous remeasured at 61 x 36 x 48 mm). There is bony destruction of the paranasal sinus walls. D. The mass extends superiorly and completely opacifies both frontal sinuses. Laterally, the mass extends to both orbits causing displacement of both medial rectus muscles, more on the right, abutting the thickened right optic nerve. There is interval resolution of the right ocular proptosis.

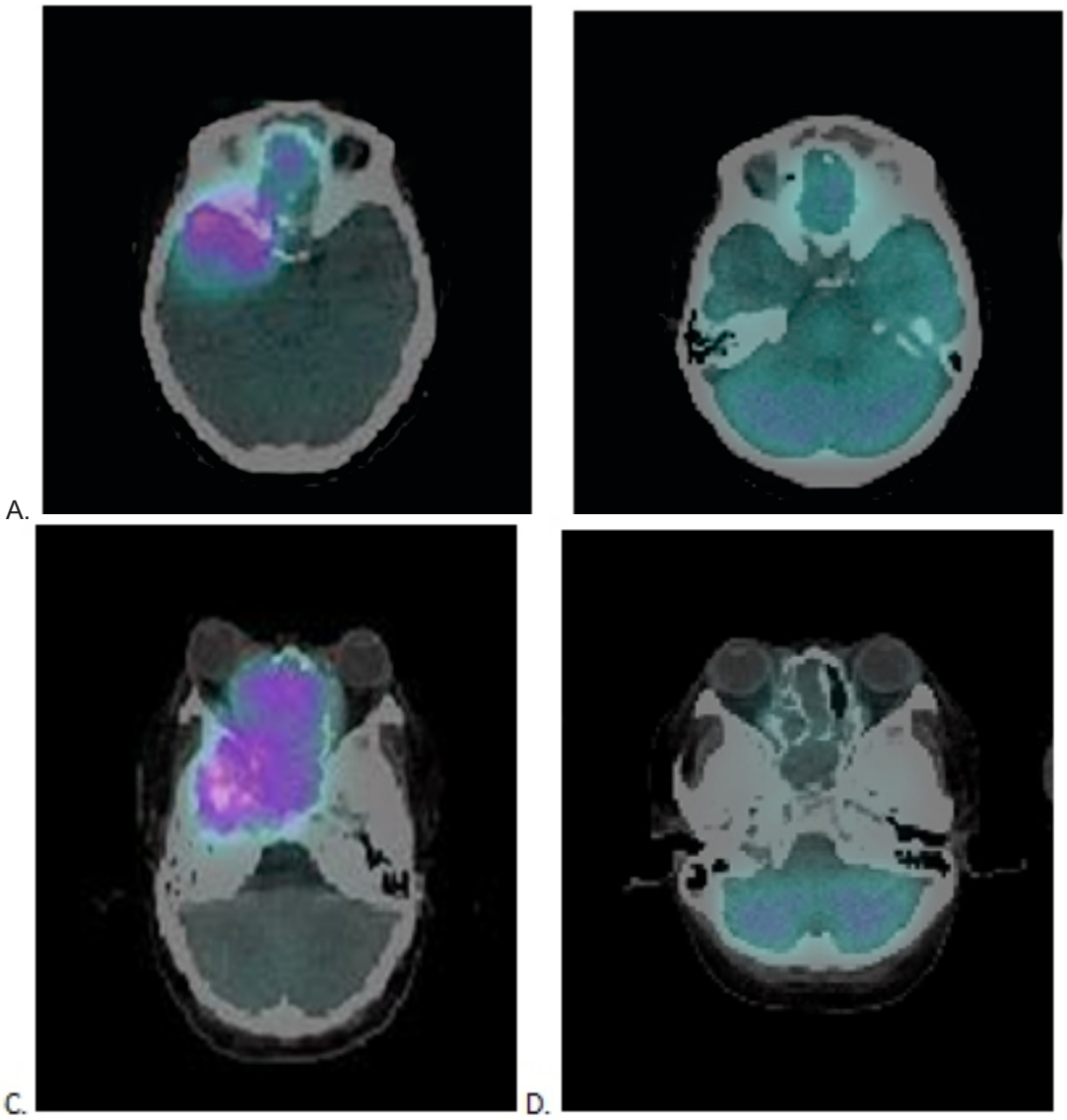

Figure 9. A comparison of the previously seen mass using repeat positron emission tomography-computed tomography (PET-CT) scan. A and C. Previously seen high metabolic activity of the mass in the nasal cavity including the orbital structures, nasopharynx, and facial bones with intracranial extension. C. The previously seen intracranial extension is no longer evident. D. Significant decrease in metabolic activity (SUV 6.1, previously 26.2) and size of the heterogeneously enhancing mass centered in the nasal cavity and ethmoid sinuses. There was also regression in the paranasal sinus extension, stable lytic changes seen in the right posterolateral maxillary sinus wall and other structures around the area.

Re-evaluation of the tumor was done after one month of completing the cycles of chemotherapy. Repeat cranial magnetic resonance imaging (MRI) with IV contrast showed a significant reduction in the size of the previously seen lobulated, heterogeneously enhancing, expansile mass occupying the nasal cavity approximately measuring 57.3 x 34.1 x 39.9 mm (AP x T x CC; previously remeasured at 61 x 36 x 48 mm). The mass extends laterally causing displacement of both medial rectus muscles, more on the right, abutting the thickened right optic nerve. There was also interval resolution of the right ocular proptosis. There were still bone destructions of the paranasal sinuses seen. There was also mass enhancement seen in the right anterior temporal and right basal frontal region.

Repeat positron emission tomography-computed tomography (PET-CT) scan with IV contrast revealed a significant regression in metabolic activity (SUV 6.1, previously 26.2) and size of the heterogeneously enhancing mass centered in the nasal cavity and ethmoid sinuses measuring 5.5 x 3.7 x 3.8 cm (previously 8.2 x 6.5 x 8.2 cm). Moreover, there was marked regression to resolution in the intracranial extension, right inferior frontal and right temporal lobe edema, right lateral ventricle compression,

subfalcine herniation, and right eye proptosis. Moreover, there was interval regression in the metabolic activity and size of the previously mentioned right level II and parapharyngeal lymphadenopathies. The rest of the body remained PET negative.

The patient was referred to ENT and Neurosurgery for evaluation and possible resection of tumor. The tumor may be resectable by surgery but will involve enucleation of the right eye. However, the patient did not consent for surgery and opted palliative care.

Discussion

For this case, routine work-up revealed a malignant round cell neoplasm in which the differential diagnoses were narrowed down using immunohistochemistry stains which were consistent with an olfactory neuroblastoma. Although chromogranin was negative which may indicate a missed type of neuroendocrine tumor and carcinoma [17], it may also be a false negative result. In a study conducted by Gut *et al.*, rapidly proliferating, poorly differentiated neuroendocrine tumors that lose their structural characteristics and have a smaller number of secretory vesicles, may not release the marker, thus the false-negative result [18].

The treatment modalities for olfactory neuroblastoma primarily include surgery, using techniques such as extracranial surgical excision, craniofacial surgical resection, and radiotherapy and chemotherapy either alone or as combination. Chemotherapy alone has not been the first choice and a combination of surgery and radiotherapy seems to be the optimal choice of treatment [19]. Table 1 summarizes our literature search for reported and published cases with intracranial extension in which most cases were treated with a combination of surgical resection and adjuvant radiotherapy that demonstrates favorable outcomes. In these case reports, most patients had promising outcomes with no recurrence for months to several years. To the best of our knowledge, as compared with these reported cases where patients were ambulatory, had intracranial extension and were resectable, the patient in this study had severe dysfunctional status due to increased intracranial pressure as the tumor was larger in size and more extensive. Thus, the tumor was unresectable at the time of presentation and so treatment using chemotherapy and radiotherapy became the plan of management.

The patient presented to us moribund (ECOG 4), hence, proceeding with the treatment plan became a dilemma that might hugely affect the outcome. Studies have shown cytoreduction using combinations of chemotherapy regimens and radiotherapy with significant response [14,16,20]. The regimen of choice for chemotherapy, which was also used in this case report, are cisplatin and etoposide in combination with radiotherapy in which patients were reported to have dramatic responses [14,16]. The first report of using concurrent chemotherapy and radiotherapy was done by Sohrabi. S., *et al.* with promising responses but with only 24 months of follow-up [21]. Mishima *et al.* also reported cases using chemotherapy in combination with radiotherapy in which they had 12 patients with adolescent-onset and adult-onset olfactory neuroblastoma that had complete responses despite reported toxicities such as electrolyte imbalances [14]. In a study conducted by Su *et al.*, majority of the patients were treated with induction chemotherapy using cisplatin and etoposide with good response (68%). Among these cases, 2 cases were treated with chemotherapy and radiotherapy. One was alive with no recurrence of disease and the other one died [22].

Treatment was done using chemotherapy and radiotherapy. Although, it was uncertain how the patient will respond to the treatment, the decision to proceed was made since she was at a young age. Treatment with chemotherapy was started at a 20% dose reduction due to her moribund state; subjecting her to a 100% dose may induce more vomiting that will further contribute to the increased intracranial pressure from the tumor. During the course of treatment, consistent functional progress was seen and the patient became self-sufficient (ECOG 1). However, the role of chemotherapy was analyzed in a study conducted by Cranmer *et al*. to which the analysis did not support chemotherapy to improve either the disease-survival rate or the overall survival [23]. Because of this, chemotherapy is always done as neoadjuvant followed by surgery or as adjuvant therapy for palliative care to metastatic cases [13]. Furthermore, a higher survival rate was observed in a study conducted by Bartel *et al.* using neoadjuvant chemotherapy obtaining 75% response rate [24].

Several studies have demonstrated an improved survival rate upon doing surgical resection after systemic therapy [14,25,26]. Thus, surgical resection was considered for the patient but will require enucleation of the right eye. Alternatively, second-line chemotherapy using vincristine, doxorubicin, ifosfamide (VAI regimen) will be done. In a study conducted by Yang *et al.*, a positive response for almost a year in remission was seen using VAI regimen every 21-day cycle with no surgical intervention and mild toxicities include nausea and neutropenia [27]. Having consented to either treatment options, it will still warrant active surveillance for the patient to have the best chance of extending her survival period.

Table 2. *Summary of reported and published cases of olfactory neuroblastoma with intracranial extension without distant metastasis in the adult population*

Case	Year	Age/Gender	Tumor Extent	Treatment	Median Follow-up /Survival	Outcome
*Fortuno, K.M., and Igot, M.O.	2020	33/F	Frontal lobe and Temporal lobe, ipsilateral level IIA, parapharyngeal nodes	NCT + NRT	12 months	Alive
*Ogawa T., *et al.*	2020	43/M	Frontal lobe	NCT + CFR + AR	7 months	Alive, no recurrence
*Su, S.Y., *et al.*	2017	39	Brain	IC + RT	48 months	Alive, no recurrence
		70	Orbit, Brain	IC + RT	97 months	Dead
		78	Orbit, Brain	NCT + CFR + ACR	44 months	Dead
		45	Dura, ipsilateral levels IA, IB, external jugular, parapharyngeal node. Contralateral level II node.	NCT + CFR	1 month	Unknown
		54	Brain	NCT + CFR + ACR	79 months	Alive, no recurrence
		61	Optic nerve, orbital apex, dura.	NCT + NRT + CFR	48 months	Alive, with recurrence
		37	Dura; ipsilateral retropharyngeal, levels IB and II, and parotid nodes	NCT + CFR + ACR	50 months	Dead
		70	Brain and dura	NCT + CFR + AR	43 months	Alive, with recurrence
		48	Brain	NCT + CFR + ACR	26 months	Alive, with recurrence
		57	Dura, orbit, orbital apex	NCT + CFR + ACR	13 months	Alive, with recurrence
Toader C. *et al.*	2018	46/F	Frontal lobe	BFC + LR + AC + AR	20 months	Alive, no recurrence
Nair, R.P., *et al.*	2016	30/F	Frontal lobe	CFR + AR	4 months	Dead
		67/F	Frontal lobe	CFR + AR	2 ½ years	Alive, no recurrence
*Kim, Y.S., *et al.*	2016	68/F	Frontal lobe	NCT + CFR + AR	5 years	Alive, with recurrence
*Giridhar, P., *et al.*	2015	39/M	Anterior cranial fossa and frontal lobes	NCT + CFR + AR	8 months	Alive, no recurrence
Sivakumar, W., *et al.*	2015	48/M	Right frontal lobe	CFR + AR + AC	11 years	Dead
		48/F	Anterior cranial fossa and frontal lobes	CFR + AR + AC	9 years	Alive, with recurrence
Sham S. *et al.*	2014	52/F	Frontal lobe	CFR + AR	4 years	Alive, no recurrence
Dunbar, E.M, *et al.*	2012	42/M	Frontal lobe	CFR + AR + AC + AAT	19 years	Dead
Lua, B.K, *et al.*	2012	40/F	Frontal base and orbital extension	CFR + AC + AR	2 years	Dead
*Sohrabi. S., *et al.*	2011	66/M	Frontal lobe	NCT + NRT + CFR	24 months	Alive, no recurrence
*Aljumaily, R.M., *et al.*	2011	46/M	Anterior cranial fossa and frontal lobes	NCT + CFR + ART	>8 months	Alive, no recurrence
Bist, S.S., *et al.*	2006	40/M	Frontal lobe with right orbital extension	CFR + AR	3 months	Alive, no recurrence
Tamase, A., *et al.*	2004	55/M	Frontal lobe, left orbit, temporal fossa	CFR + AR	5 years	Alive, with recurrence
*Liu, J.K. *et al.*	2003	58/F	Frontal lobe	NCT + NRT + CFR	8 months	Alive, no recurrence
Kenmochi, M. *et al.*	2003	44/F	Left frontal base	CFR + AT	11 years	Alive, no recurrence
Tatagiba, M., *et al.*	1995	50/F	Anterior cranial fossa	CFR + AR	7 years	Alive, no recurrence
		70/M		CFR only	18 months	Dead
		29/F		CFR only	5 years	Alive, with recurrence
		47/F		CFR + AR	6 months	Alive, with recurrence
		52/F		NRT + CFR + AR	5 ½ years	Alive, no recurrence
		54/F		CFR only	4 ½ years	Alive, no recurrence
		55/M		CFR + AR	18 months	Alive, with recurrence
		55/M		CFR + AR	4 ½ years	Alive, no recurrence
Meneses, M. S., *et al.*	1990	59/F	Frontal lobe	BFC + AR	4 years	Alive, with recurrence
		58/F	Frontal lobe, Subdural and orbital extension	CFR + AR + AC	10 months	Dead
		38/F	Frontal lobe and orbital extension	NRT + CFR	8 months	Alive, no recurrence
Rodas. R. A., *et al.*	1986	46/M	Left frontal lobe	CFR + RT + AC	2 years	Alive, with recurrence

*Cases treated with neoadjuvant chemotherapy
Abbreviations: NCT: Neoadjuvant chemotherapy, NRT: Neoadjuvant Radiation therapy, CFR: Craniofacial resection; RT: Radiation Therapy; BFC: Bifrontal Craniotomy; LR: Lateral Rhinotomy; AC: Adjuvant chemotherapy; AR: Adjuvant radiotherapy; AAT: Anti-angiogenic therapy; IC: Induction Chemotherapy; ACR: Adjuvant Chemoradiotherapy.

Conclusion

This study reports a rare case of olfactory neuroblastoma which was diagnosed at an advanced stage due to fear of getting infected during the COVID-19 pandemic. This case report shows the significance of chemotherapy with radiotherapy as treatment of choice for advanced stage olfactory neuroblastoma in patients with very large tumors and severe dysfunctional status to which resection is not amenable but still feasible to treat than palliative care. Although the chemotherapy regimens for olfactory neuroblastoma are still being studied and the best treatment option is still to be determined, patients with olfactory neuroblastoma may be highly sensitive to chemotherapy with radiotherapy and it might be the best option for unresectable tumors, recurrence, and even on late-stage disease. However, chemotherapy alone may not be a sufficient modality to achieve long-term improvement in survival. Hence, a multidisciplinary approach is recommended. More studies are needed to determine the best approach for these kinds of patients.

Ethical Considerations

A written informed consent was obtained from the patient and patient representative for publication of this case report and the accompanying images.

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