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Case Report

A case of neurofibromatosis type 1 with clival chordoma

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ABSTRACT

Neurofibromatosis type-1 is an autosomal dominant tumour syndrome with a high clinical susceptibility to malignancies, especially nervous system malignancies. Here, we reported a case of neurofibromatosis type-1 in a male in his 50s, who presented with generalised weakness, headache associated with ear pain, a feeling of heaviness of the head, and giddiness for a duration of 1 week. On examination, he had axillary freckling and multiple neurofibromas over his body. Nystagmus and dysdiadokokinesia were present. MRI brain revealed an enhancing lesion in the sphenoid and clivus, extending into the sellar and supra-sellar region. The possibility of pituitary adenoma and clival chordoma were considered. He was referred to Neurosurgery and underwent Trans-nasal Trans-sphenoidal near-total resection of the tumour. Biopsy of the lesion was indicative of conventional clival chordoma, which is rarely reported with NF-1. The post-operative period was uneventful and the patient is planned for regular follow-up to detect recurrence.

Keywords: Neurofibromatosis type-1, Clival chordoma, Neurofibromatosis, von Recklinghausen disease

INTRODUCTION

Neurofibromatosis type-1 (NF-1), formerly known as von Recklinghausen disease, is a neuroectodermal abnormality that exhibits an autosomal dominant inheritance, with an incidence of about 1 in 3,500 individuals. The manifestations of NF-1 include axillary and inguinal freckling, cafe-au-lait spots or macules, cutaneous neurofibromas along peripheral nerves and iris hamartomas (Lisch nodules).[1,2]

The incidence of malignancies in NF-1 is high, with optic gliomas and astrocytomas being the most common.[3] Therefore, symptoms such as headache, weakness of limbs, and earache, as seen in our patient, should always be thoroughly evaluated to rule out intracranial lesions.

Chordomas are rare tumours which occur predominantly in the sacrum, skull base, and spine and have a notoriously high rate of recurrence.[4,5] Their association with NF-1 is not well established.

The co-existence of a clival chordoma with NF-1 in the sphenoidal fossa is an interesting differential to consider, along with pituitary macroadenoma, astrocytoma, and other more common tumours seen in NF-1. Follow-up and imaging become extremely important in such cases due to the rate of recurrence in chordomas, and the possibility of developing other CNS tumours in the future.

CASE REPORT

A man in his 50s, with a history of NF-1 presented with complaints of insidious onset of generalised weakness, holocranial headache and ear pain, heaviness of the head, and giddiness for 1 week. He gave no history of blurring of vision, retro-orbital pain, stiffness of the neck or seizures. However, he did complain of decreased vision in the last 3 months and gave a history of tubular vision with an inability to see objects in his peripheries. He was diagnosed with NF-1 in childhood with nodular swellings over his body since birth, which gradually increased in size and number. He had poor performance in school and difficulty verbalising and had had slurring of speech since a young age. No similar complaints were reported in his family and there was no history of consanguineous marriage between his parents.

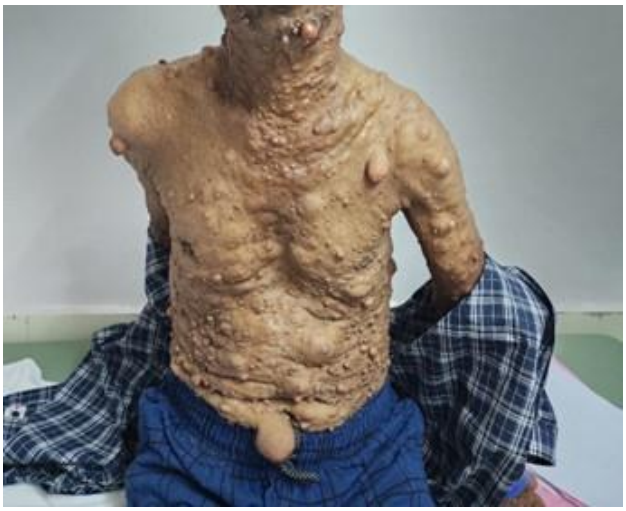

Figure 1: Patient with multiple neurofibromas present over his body.

Figure 2: (A) Sagittal section of pre-operative MRI Brain showing hyperintense, minimally enhancing lesion in sellar and suprasellar regions (red arrow) compared with (B) Sagittal section of post-operative CT.

On examination, the patient was conscious and oriented, and his vitals were stable. Macroglossia was present. Multiple nodular swellings were present all over his face, thorax, and limbs ranging from 0.5 cm to 5 cm in diameter. The nodules were variable in consistency with some lesions being hard and non-mobile, and some cystic and fluctuant (Figure 1). A large outgrowth was seen hanging from mid-thorax level over the left side of his back and was cystic in consistency. Axillary freckling was seen bilaterally. No café au lait spots were present. Bilateral radial nerve thickening was present. No fibromas, tuft of hair, gibbus or knuckling were present over the spine. The patient had dysarthria and slurred speech, which were present since childhood. Nystagmus was noted on right lateral gaze and dysdiadokokinesia was present. Romberg's sign was negative.

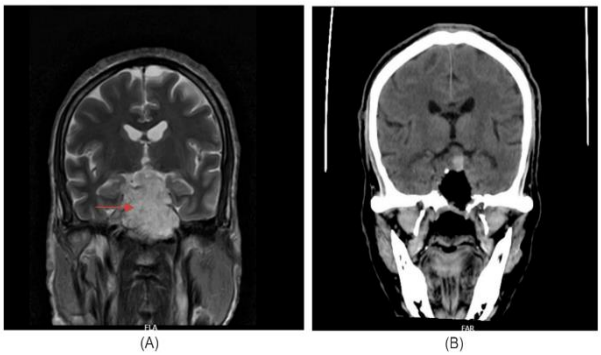

Figure 3: (A) Coronal section of pre-operative MRI brain showing hyperintense, minimally enhancing lesion in sellar and suprasellar regions (red arrow) compared with (B) Coronal section of post-operative CT.

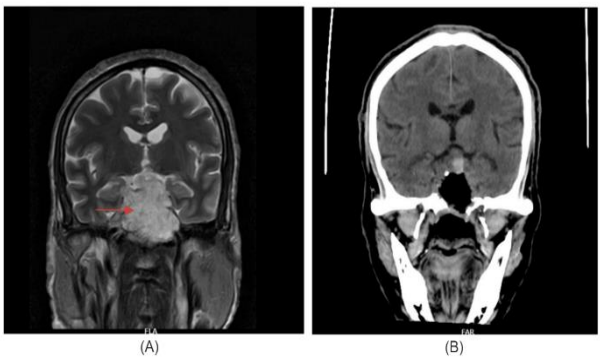

Figure 4: Coronal (A) and Axial (B) sections of CT cerebral angiogram showing a hypodense mass lesion (red arrows).

Lab investigations showed hypocortisolism that responded to the ACTH stimulation test. The patient also had elevated prolactin of 26 ng/ml while his other hormones were within normal reference limits. All his other laboratory investigations were within normal limits.

Ophthalmological evaluation was done which showed no evidence of any intraorbital compression. Exophthalmometry as well as color vision testing were normal. Goldmann perimetry testing was attempted but the patient was not cooperative.

MRI brain done initially showed an ill-defined T1 iso-hypo, T2/FLAIR hyperintense lesion that was minimally enhancing in sellar and suprasellar regions measuring 3.3×3.4×3.9 cm (Figure 2). Pituitary gland, optic chiasma, and hypothalamic structures were not seen separately from the lesion. Superiorly, the lesion extended into the 3rd ventricle while posteriorly it extended into the interpeduncular cistern and indenting on the pons. The lesion was encasing the left ICA and was closely related to right ICA. The lesion showed diffusion restriction. However, it showed normal contrast opacification. On MRS the lesion showed decreased NAA peak and elevated choline peak. Based on these findings, the possibility of optic pathway glioma was considered. Figure 2 and 3 compare pre-operative MRI brain with above findings with post-operative CT.

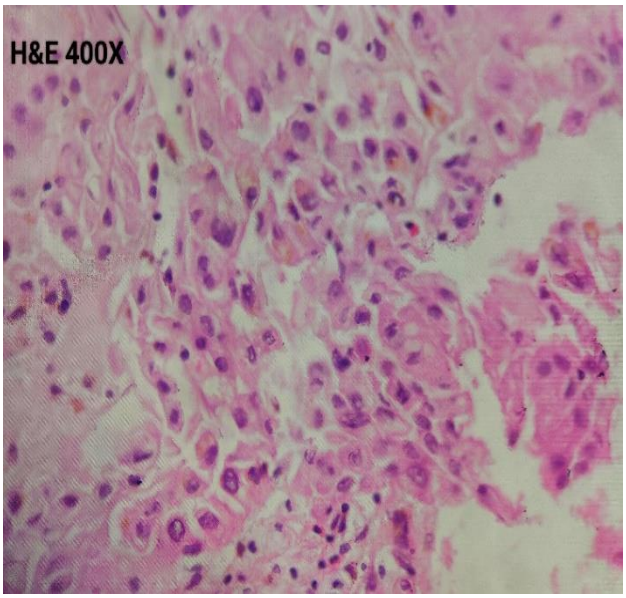

Figure 5: Photomicrograph shows tumor nests composed of large cells with oval to round nuclei and abundant clear to vacuolated cytoplasm (physaliphorous cells).

CT cerebral angiogram showed a hypodense mass lesion with epicenter in sphenoid sinus showing interspersed hyperdense foci (Figure 4). It extended anteriorly and was invading the bilateral posterior ethmoidal sinuses, inferiorly involving the sellar space and causing expansion and erosion of the sella turcica, lateral extending into the parasellar regions and eroding the greater wings of the sphenoid bone and petrous part of the temporal bone, displacing and encasing the cavernous segment of left ICA, however caliber and contrast opacification were maintained. Posteriorly was invading the clivus and causing its erosion and abutting the left hemipons. Posteriorly, it was also abutting the basilar artery at the bifurcation and the P1 segments of bilateral PCA, however the arteries showed normal contrast opacification. Findings were hence suggestive of neoplastic etiology.

The patient underwent near total resection of sellar and supra sellar mass via extended basal approach, trans nasal, trans sphenoidal approach. Biopsy and microscopy of the specimen showed a fragmented lobulated tumor with infiltrating bony trabeculae composed of small lobules and nests of tumor cells with round to oval nuclei (Figure 5). Nuclei showed focal nuclear pleomorphism and abundantly clear to eosinophilic cytoplasm with cytoplasmic vacuolation (physaliphorous cells) in a myxoid and pseudo chondroid matrix. Focal spindle cells were also seen with sparse perilobular lymphocytic infiltrate. The findings were indicative of a diagnosis of conventional chordoma.

Post-operative CT was unremarkable with no post-operative cavity bleed. The patient was kept in the ICU for 1 day for observation to detect rhinorrhea. He was monitored further, adequately mobilised, and once he showed clinical improvement, discharged with a prescription of oral prednisolone 5 mg in the morning and 2.5 mg in the evening.

Table 1: NIH diagnostic criteria for NF-1 applied to our patient.[2]

S. no.	The patient should have 2 or more of the following 7 criteria	Present/absent in our patient
1	Café au lait spots- 6 or more (>5 mm pre-puberty, >1.5 mm post-puberty)	Absent
2	Neurofibromas- 2 or more of any kind; Plexiform neurofibroma- 1 or more	Present
3	Axillary or groin freckling	Present
	Optic glioma	Absent
4	Lisch nodules- 2 or more	Absent
5	Dysplasia of sphenoid or thinning of long bone cortex	Absent
6	First-degree relative with NF-1	Absent

On follow-up after 2 weeks and 1 month, the patient reported no fresh complaints and reported improvement in symptoms. He is planned for regular follow-up and screening.

DISCUSSION

The diagnosis of NF-1 is clinical, based on criteria prescribed by the National Institute of Health on the basis of most frequent disease manifestations such as Lisch nodules, Café au lait macules, neurofibromas and axillary freckling as well as disease complications common in NF1.[2] At least two of their seven criteria should be present to make a diagnosis (Table 1).

Genetically, neurofibromatosis type-1 arises from mutations occurring on the NF-1 gene. This gene is

located on chromosome 17q11.2 and encodes for neurofibromin, a protein that activates ras GTPase. This downregulates the Ras signalling pathway thereby controlling cellular proliferation and acting as a tumor suppressor.[1,6]

Hence, NF-1 is a major risk factor for the development of malignancy. Therefore, any brain lesions in NF-1 patients must be closely monitored due to this high clinical susceptibility to malignancies. Benign brain lesions such as pilocytic astrocytomas and optic gliomas make up the majority of intracranial neoplasms in NF-13, however, cases of glioblastoma and high-grade astrocytomas have also been recorded.[7-9]

The association between NF-1 and chordomas is not well established. A literature search on PubMed showed no similar cases in which a clival chordoma was associated with NF-1. Chordomas are rare tumours with an incidence of 0.08 per 100,000 individuals, constituting 0.2% of intracranial tumours.[10,11] They have been associated with alterations in the brachyury gene and other genetic factors.[12-14] Chordomas are postulated to arise from remnants of the notochord and are found to have a predilection for the axial skeleton. The most common sites where chordomas arise from are the sacrum, skull base, and spine.[4] It is plausible that the genetic predisposition in NF1 patients may increase the risk of developing chordomas, although further research is needed to establish a definitive link.

Chordomas have a high rate of recurrence, even after multiple surgeries.[5] NF1 patients already have an increased susceptibility to developing other malignancies. The presence of a chordoma in a patient with NF1 raises questions regarding the underlying genetic predisposition and potential future tumour development. Therefore, it is essential to consider the long-term implications and prognosis for patients with NF1 and clival chordoma.

Long-term surveillance and close follow-up are crucial for early detection and management of any potential tumour recurrence or new tumour development

CONCLUSION

NF-1 is found to be a major risk factor for the development of malignancies, hence any signs and symptoms suggestive of neoplastic etiology should be treated with high suspicion and properly investigated. Commonly seen intracranial lesions in NF-1 patients are optic gliomas and astrocytomas, but various other lesions are reported to be associated with them. Clival chordomas are very rare tumours and are found to have a high rate of recurrence. This especially highlights the importance of close follow-up to detect such recurrence. Long-term surveillance and follow-up is essential for detection of recurrence or development of new malignancies.

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