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CLINICAL CASE REPORT

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Plexiform Neurofibroma

A Case Report

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Abstract: Plexiform neurofibromas represent an uncommon variant (30%) of neurofibromatosis type 1 (NF-1) in which neurofibromas arise from multiple nerves as bulging and deforming masses involving also connective tissue and skin folds.

We report a rare case of a 30-year-old man who presented with a progressive facial deformity that began in early childhood. Skin examination also revealed multiple neurofibromas and café-au-lait macules on the trunk and arms. Histopathological examination on biopsy samples showed overgrowth of peripheral nerve components and connective tissue. Two diagnostic criteria for NF-1 (plexiform variant) were met, the patient did not accept to undergo genetic testing. Craniofacial MRI confirmed the presence of a deforming mass arising from the left side of his face giving homolateral eye dislocation.

Surgery is the mainstay of the treatment. However, the patient expressed the preference to avoid surgery and chose to undergo clinical follow-up every 6 months.

Diagnosis of plexiform neurofibromas is usually made clinically, especially if classical hallmarks of NF-1 are present. Therapy is surgical, aiming at resecting deforming masses and cancerous tissue when malignant transformation occurs.

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Abbreviations: IGFBP1 = insulin-like growth factor binding protein 1, MPNST = malignant peripheral nerve sheath tumors, NF-1 = neurofibromatosis type 1, RANTES = regulated upon activation, normal T-cell expressed and secreted.

INTRODUCTION

Neurofibromatosis type 1 (NF-1) is a rare autosomal dominant genetic condition (1/3000 subjects), caused by mutations of the *NF1* gene, which is located at chromosome 17q11.2, characterized by multiple skin alterations such as café-au-lait macules and axillary freckling and by tumoral growth along nerves, called neurofibromas.[1] Plexiform neurofibromas represent an uncommon variant of NF-1 in which neurofibromas arise from multiple nerves as bulging and deforming masses involving also connective tissue and skin folds—hence the clinical description of lesions as ''bags of worms.'' We report a rare case of plexiform neurofibroma, arising from cranial nerves, which presented also with classical hallmarks of NF-1 disease. Finally, we discuss clinical findings, diagnosis, and therapy of this rare deforming disorder.

PATIENT INFORMATION AND DIAGNOSTIC ASSESSMENT

A 30-year-old man was referred for evaluation of a progressive facial deformity that began in early childhood (at around 2 years of age). His medical history was unremarkable and none of the relatives was known to be affected.

On physical examination the left side of his face was deformed by a bulging and soft mass involving the eyelids, cheek, and nose; also the lips and chin were affected, with sparing of the forehead and right side (Figure 1A). The patient was unable to open his left eye due to overhanging folds involving the eyelids. However, the mass did not result in vision impairment or speech difficulties. Skin examination also revealed multiple neurofibromas and café-au-lait macules on the trunk and arms (Figure 1B; straight and curved arrows, respectively).

Routine laboratory tests were normal. Histopathological examination on biopsy samples showed overgrowth of peripheral nerve components and connective tissue (Figure 2 A–D).

Craniofacial MRI confirmed the presence of a deforming mass arising from the left side of his face giving homolateral eye dislocation (Figure 3A and B).

Two diagnostic criteria for NF-1 (plexiform variant) were met.[2] The patient did not accept to undergo genetic testing.

DISCUSSION

Plexiform neurofibromas occur in up to 30% of cases of NF-1, most frequently in the craniomaxillofacial region. These lesions manifest early in life and tend to transform to malignant peripheral nerve sheath tumors (MPNST).[3] Malignant progression is generally considered the main cause of mortality, occurring in 2% to 16% of cases.[3]

Craniomaxillofacial lesions can be divided into massive plexiform, cranioorbital, and cervical neurofibromas.[4] Different clinical presentations can be observed, depending on the prevalent clinical locations. The main symptoms are ocular motility disturbances from eye involvement, dyspnea and respiratory failure from upper airway compression, neurological deficits from cranial nerve compression, and social deprivation,

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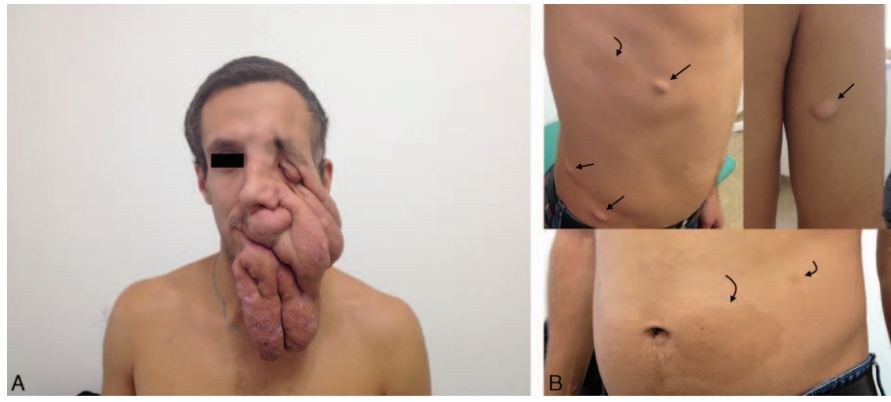

FIGURE 1. (A) Severe disfiguration of the left side of the face, due to overhanging folds of skin affecting the temporal, orbital, and cheek areas. Overhanging folds affecting the eyelids dislocated the eye inferiorly. (B) Multiple neurofibromas and café-au-lait macules located on the trunk and arms.

depression and other mood disorders resulting from facial disfigurement.[5]

Diagnosis of NF-1 is usually achieved when 2 or more criteria, developed by the National Institutes of Health (NIH), are met.[2] Plexiform neurofibromas are generally diagnosed clinically with appreciation of the typical features, and histopathology is useful to exclude malignant transformation. Prenatal testing may be used to identify the existence of the NF-1 mutation in the fetus.[5] Preimplantation genetic diagnosis could be used as screening method for NF-1 in embryos produced via in vitro fertilization, while chorionic villus sampling or amniocentesis can be used to detect NF-1 in the fetus.[5]

Recently, some authors have identified four markers (epidermal growth factor receptor, interferon-γ, interleukin-6, and tumor necrosis factor-α) to distinguish between patients with NF-1 and healthy subjects, and 2 additional markers as potential early risk predictors of developing MPNST (insulin-like growth factor binding protein 1 (IGFBP1)) and regulated upon activation, normal T-cell expressed and secreted (RANTES). The authors have found significantly higher concentrations of these

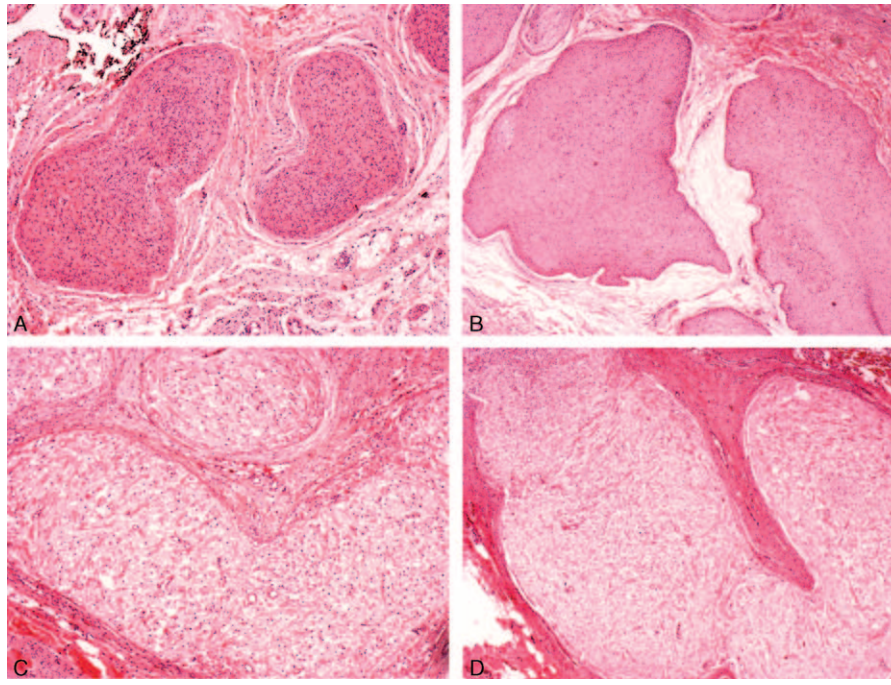

FIGURE 2. Histopathological findings of plexiform neurofibroma. (A) Cylindrical enlargement of subcutaneous nerves, containing large nerve fascicles (hematoxylin and eosin, original magnification 20×). (B) Irregularly contoured, enlarged subcutaneous nerves are identified, containing large nerve fascicles. (Hematoxylin and eosin, original magnification 20×). (C) Higher power view, showing cylindrical enlargement of subcutaneous nerves. In addition to nerve fascicles, a cellular matrix containing fibroblasts, Schwann cells, collagen, and mucin is shown. This proliferation is contained within the epineurium of the involved nerves (hematoxylin and eosin, original magnification 40×). (D) This view shows a particularly enlarged subcutaneous nerve. Again, nerve elements, Schwann cells, fibroblasts, collagen, and mucin are confined within the epineurium of the involved nerve (hematoxylin and eosin, original magnification 40×).

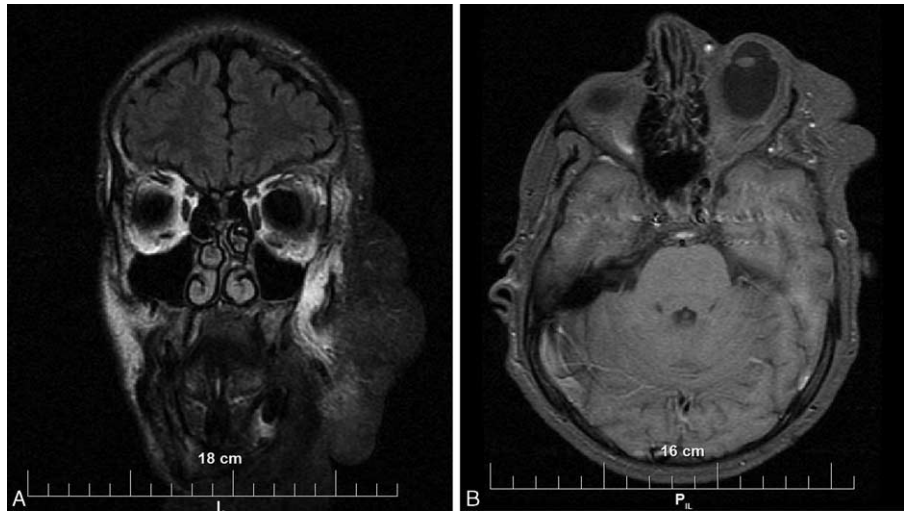

FIGURE 3. Craniofacial MRI. (A) Axial view: deforming plexiform neurofibroma arising from the left side of the face giving (B) coronal view: homolateral eye dislocation.

markers in patients with NF-1 and MPNST as compared to those without.[6] These data suggest a screening role of these biomarkers in patients with clinical variants of NF-1 (eg, plexiform neurofibromas) that are at high risk of malignant transformation.[6]

Therapy of plexiform neurofibromas is usually surgical, aiming at resecting deforming masses and cancerous tissue when malignant transformation occurs. However, these masses tend to recur in 20% of cases despite an appropriate approach.[7]

In unresectable, progressive and symptomatic lesions, good results have been reported recently after the administration of interferon-α.[4,8] However, the prognosis is still unpredictable due to the high risk of progression of the disease and its variable expressivity.[6]

PATIENT OUTCOME

In this case, normal living was limited due to the severe facial disfigurement as the result of progression of the disease. The mass is still growing. Despite this, the patient expressed the preference to avoid surgery and chose to undergo clinical follow-up every 6 months. Systemic therapy with interferon-α has been discussed as a possible future option.

REFERENCES

1. Evans DG, Howard E, Giblin C, et al. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet A.* 2010;152A:327–332.
2. Neurofibromatosis. *NIH Consens Statement.* 1987 Jul 13-15 [cited year month day];6(12):1–19.
3. Sabatini C, Milani D, Menni F, et al. Treatment of neurofibromatosis type 1. *Curr Treat Options Neurol.* 2015;17:355.
4. Citak EC, Oguz A, Karadeniz C, et al. Management of plexiform neurofibroma with interferon alpha. *Pediatr Hematol Oncol.* 2008;25:673–678.
5. Ferner RE, Gutmann DH. Neurofibromatosis type 1 (NF1): diagnosis and management. *Handb Clin Neurol.* 2013;115:939–955.
6. Park SJ, Sawitzki B, Kluwe L, et al. Serum biomarkers for neurofibromatosis type 1 and early detection of malignant peripheral nerve-sheath tumors. *BMC Med.* 2013;11:109.
7. Needle MN, Cnaan A, Dattilo J, et al. Prognostic signs in the surgical management of plexiform neurofibroma: the Children's Hospital of Philadelphia experience, 1974–1994. *J Pediatr.* 1997;131:678–682.
8. Kebudi R, Cakir FB, Gorgun O. Interferon-α for unresectable progressive and symptomatic plexiform neurofibromas. *J Pediatr Hematol Oncol.* 2013;35:e115–e117.