Surgical Neurology International

SNI: Spine, a supplement to Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor: Nancy E. Epstein, MD Winthrop University Hospital, Mineola, NY, USA

Neurofibromatosis type 1 and pregnancy: The transformation of a nodular to cystic neurofibroma in the cervical region

Rodrigo Ramos-Zúñiga, Daniel Alexander Saldaña-Koppel[1]

Department of Neurosciences, Institute of Translational Neurosciences, CUCS University of Guadalajara, [1]Department of Neurosciences, CUCS University of Guadalajara, Jalisco, México

E-mail: *Rodrigo Ramos-Zúñiga - rodrigor@cencar.udg.mx; Daniel Alexander Saldaña-Koppel - daniel.saldanak@gmail.com
*Corresponding author

Received: 19 February 15 Accepted: 16 August 15 Published: 08 October 15

Abstract

Background: The peripheral hallmarks of neurofibromatosis type 1 (NF1) are Café au lait and solid nodular neurofibromas. The morphological behavior of these lesions could be susceptible to modification during pregnancy. The present case report describes a case of cystic transformation of a nodular neurofibroma, with progressive growth and mass effect in the anterior cervical region, which was surgically resolved without any complications.

Case Description: A 33-year-old female patient with a known personal history of NF1, with annual control of the peripheral neurofibromas and cerebral and spinal magnetic resonance imaging follow-ups. Under genetic counseling, she decides to get pregnant following all the medical advises. Once the pregnancy is confirmed, she starts to notice the growth of one of them adjacent to the left cervical region. Such neurofibroma presented with the progressive gradual increase and in the last month, she presented dysphagia, dysphonia, and postural pain localized by the mass effect. Once the pregnancy concluded, the microsurgical approach was scheduled for resection of the lesion, where a cystic mass was found within the walls of the neurofibroma. The resection was uneventful.

Conclusion: The transformation of a nodular to cystic neurofibroma during pregnancy is a very rare presentation, which may exacerbate the clinical symptomatology depending on the topography of the lesion due to the mass effect it may create. This condition may alert to the recommendations and vigilance in patients with NF1, who are pregnant or are planning on a future pregnancy. The neurosurgical resolution in this region is safe and beneficial.

Key Words: Microsurgery, neck dissection, neurofibromatosis type 1, neuropathology, pregnancy

Access this article online

Website: www.surgicalneurologyint.com

DOI: 10.4103/2152-7806.166889

Quick Response Code:

INTRODUCTION

Neurofibromatosis type 1 (NF1) is one of the genetic neurocutaneous syndromes that has a greater number of phenotypic expressions.[7,11] NF1 is an autosomal dominant genetic disorder with an incidence of approximately 1 × 3500 people worldwide. About one-half of the cases are hereditary due to a mutation in the *NF1* gene; the remainders are the result of *de novo* mutations.[4,8]

How to cite this article: Ramos-Zúñiga R, Saldaña-Koppel DA. Neurofibromatosis type 1 and pregnancy: The transformation of a nodular to cystic neurofibroma in the cervical region. Surg Neurol Int 2015;6:S487-9.
http://surgicalneurologyint.com/Neurofibromatosis-type-1-and-pregnancy:-The-transformation-of-a-nodular-to-cystic-neurofibroma-in-the-cervical-region/

The clinical criteria for the disease are determined by the presence of six or more café-au-lait macules, >5 mm in prepubertal patients and >15 mm in postpubertal patients, two or more neurofibromas of any type, at least one plexifrom neurofibroma, optical gliomas, two or more Lisch nodules, sphenoid wing dysplasia, and pseudoarthrosis.[11-13] The genetic diagnosis of the NF1 gene mutation has also been recently added to the diagnostic criteria.[12] Other clinical components that are considered part of the disease are short stature, scoliosis, attention deficit disorders, language, and learning disorders. The malignant transformation of a neurofibroma is reported in approximately 10–13% of all the cases.[3]

The NF1 gene encodes neurofibromin, a tumoral suppressor protein.[11] NF1 gene is located in chromosome 17q11.2; it is conformed of 57 constitutive exons and 4 alternative ones.[1,11] The mutation observed in 50% of the new sporadic cases are due to a *de novo* mutation, and 80% of these have a paternal origin.[5] However, almost all microdeletions are of maternal origin.[15] The penetrance of this disease is 100%.

CASE REPORT

The patient is a 33-year-old female patient with personal history of NF1 (without any family history in the two previous generations) characterized by multiple Café au lait macules and multiple neurofibroma nodules in distinct regions of the skin which involve the scalp, neck, back, abdomen, and all the extremities.

The patient has a normal evolution of her disease with no incidents; she is an independent professional and refers no other symptomatology. Eventually, she complains of pain due to the mechanical compression of one of the neurofibromas. After considering the genetic counseling, the patient decides to get pregnant. During the second trimester of her pregnancy, she started to note gradual and progressive growth of one of the neurofibromas located in the anterolateral left portion of the neck, in the angle formed by the thyroid gland and the common carotid artery. Such growth gradually increased to the point where by the end of the pregnancy it had a diameter of approximately 10 cm × 15 cm, it made swallowing difficult, dysphonia, and generated local pain (nonneuropathic pain) [Figure 1]. The consistency was smooth in the peripheral contours, but firm in the center, mobile, and no skin changes were noted. She has an uneventful full term pregnancy with a C-section delivery.

After neuroimaging evaluation, a surgical approach is decided 3 months after the C-section using general anesthesia and microsurgical dissection. A tumor mass was identified, with a superficial wall, free from vascular or cervical major nerve structures, with a clear serous liquid content that after decompression, modifies the tumoral morphology immediately, allowing identification of the layers of the cystic lesion. The visceral portion of the capsule was found attached to the external plane of the thyroid gland and to the carotid artery adventitia, which was preserved. The postsurgical evolution was normal, without any complications. There were no alterations regarding phonation or deglutition, and there was a normal recovery of the external anatomy of the neck without any evidence of tumoral mass. The analysis of the fluid reported no cytological alterations and culture was negative for infection. The hematoxylin and eosin stain shows the presence of neoplastic cells, nuclear and diffuse cytoplasmic positivity to S-100 protein [Figure 2].

DISCUSSION

The interaction of neurofibromin with other membrane cellular proteins such as proteoglycans, intermediate actin filaments, and tubulin;[2] promotes the alteration in the regulation that leads to the development of the syndrome, same that along with other neurodevelopmental disorders have been denominated

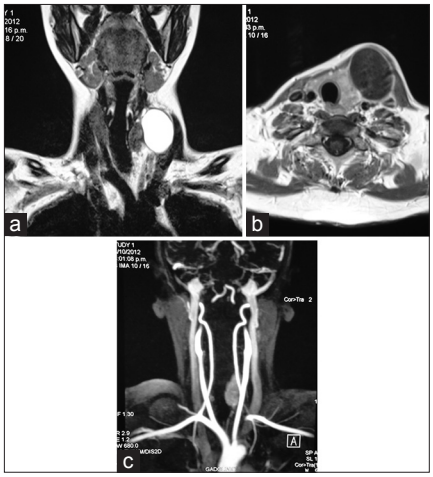

Figure 1: Magnetic resonance imaging and angiomagnetic resonance imaging. (a and b) Magnetic resonance imaging shows a cystic tumor in the left anterior cervical region creating mas effect over the midline structures. (c) There is no evidence of intramural vascular flow in the angiomagnetic resonance imaging

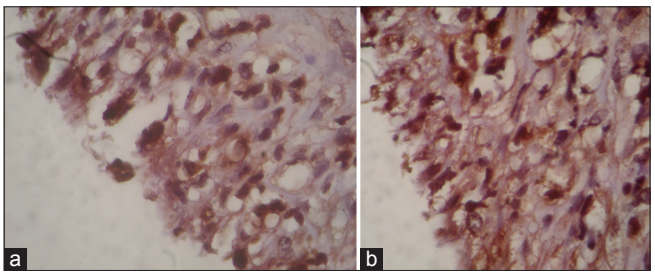

Figure 2: (a and b) The immunohistochemistry with S-100 protein shows the positive neoplastic cells in the limits of the tumoral wall (×40)

RASopathies, in relation to the identified mutations which encode for the RAS/mitogen-activated protein kinase pathway which is activated from the protein kinase pathway.[14] The NF1 gene is considered a gene suppressor which when altered does not produce enough neurofibromin to assure and regulate cellular growth (haploinsufficiency).[7] However, many cases require a second event (second-hit), which contributes to the formation of the tumors called neurofibromas. These second-hit mutations contribute to the manifestation of many of the clinical signs of the disease, in what has been considered a bi-allelic inactivation demonstrated in the neurofibromas, but is also evident in some other variants such as the presence of glomus and the tumorigenesis where the differentiation of schwann cells is affected.[9,10]

A recent theory that aims to validate the determined changes by the second mutations, which has been described in hormonal events such as puberty and pregnancy, has been described through the demonstration of a multipotential progenitor NF1 +/− cell, which is capable of *in vitro* differentiation into the different cells types found in neurofibromas, including schwann cells, fibroblasts and epithelial cells.[6] This condition may explain the influence of epigenetic factors in the transformation of the different cellular linages that a neurofibroma might express.

This condition partially explains one of the fundamental reasons for why, in the study case, pregnancy, and the own trophic factors were determining variables in the volume growth of the neurofibroma starting on the first trimester and it also reassures the tendency of the growth heterogeneity not derived directly from the proliferation of schwann cells to express as a solid tumor, but from other cellular linages such as mast cells, fibroblasts, adipocytes, and epithelial cells which generate a liquid material, that was finally responsible for the volumetric expansion of the tumor creating mass effect.

The growth and mass effect of a neurofibroma during puberty or pregnancy is a condition that should be monitored due to the possibility of the appearance of new symptoms in patients diagnosed with NF1.[13] If such symptoms develop and it is found in a surgically accessible plane, surgical resection should be considered.

The transformation of a cystic neurofibroma is rarely described in the literature; hence, this case represents minor complexity in the surgical approach. The planning and surgical strategy is similar to the carotid glomus surgical approach. The preservation of the adjacent vascular and neural structures is mandatory.

CONCLUSION

The stable patients diagnosed with NF1, can experiment some changes due to epigenetic factors that may second the mutation and modify the phenotypic expression. Such is the case in puberty and pregnancy due to the presence of trophic hormonal factors that may activate the cellular linage differentiation in the neurofibroma and contribute to its growth, whether it's solid or cystic. The surgical approach evaluating the risk/benefit is the most appropriate conduct for the resolution of the mass effect.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Bollag G, McCormick F, Clark R. Characterization of full-length neurofibromin: Tubulin inhibits Ras GAP activity. EMBO J 1993;12:1923-7.
2. Bonneau F, D'Angelo I, Welti S, Stier G, Ylänne J, Scheffzek K. Expression, purification and preliminary crystallographic characterization of a novel segment from the neurofibromatosis type 1 protein. Acta Crystallogr D Biol Crystallogr 2004;60(Pt 12 Pt 2):2364-7.
3. Evans DG, Baser ME, McGaughran J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet 2002;39:311-4.
4. Huson SM, Compston DA, Clark P, Harper PS. A genetic study of von Recklinghausen neurofibromatosis in south east Wales. I. Prevalence, fitness, mutation rate, and effect of parental transmission on severity. J Med Genet 1989;26:704-11.
5. Jadayel D, Fain P, Upadhyaya M, Ponder MA, Huson SM, Carey J, *et al.* Paternal origin of new mutations in von Recklinghausen neurofibromatosis. Nature 1990;343:558-9.
6. Jouhilahti EM, Peltonen S, Callens T, Jokinen E, Heape AM, Messiaen L, *et al.* The development of cutaneous neurofibromas. Am J Pathol 2011;178:500-5.
7. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The pathoetiology of neurofibromatosis 1. Am J Pathol 2011;178:1932-9.
8. Lammert M, Friedman JM, Kluwe L, Mautner VF. Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. Arch Dermatol 2005;141:71-4.
9. Legius E, Marchuk DA, Collins FS, Glover TW. Somatic deletion of the neurofibromatosis type 1 gene in a neurofibrosarcoma supports a tumour suppressor gene hypothesis. Nat Genet 1993;3:122-6.
10. Maertens O, Brems H, Vandesompele J, De Raedt T, Heyns I, Rosenbaum T, *et al.* Comprehensive NF1 screening on cultured Schwann cells from neurofibromas. Hum Mutat 2006;27:1030-40.
11. Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type 1 (NF1). J Med Genet 1996;33:2-17.
12. Stumpf D, Alksne J, Annegers J, Brown S, Conneally P, Housman D, *et al.* Neurofibromatosis. Conference statement. National Institutes of Health Consensus Development Conference. Arch Neurol 1988;45:575-8.
13. Terry AR, Barker FG 2nd, Leffert L, Bateman BT, Souter I, Plotkin SR. Neurofibromatosis type 1 and pregnancy complications: A population-based study. Am J Obstet Gynecol 2013;209:46.e1-8.
14. Tidyman WE, Rauen KA. The RASopathies: Developmental syndromes of Ras/MAPK pathway dysregulation. Curr Opin Genet Dev 2009;19:230-6.
15. Upadhyaya M, Ruggieri M, Maynard J, Osborn M, Hartog C, Mudd S, *et al.* Gross deletions of the neurofibromatosis type 1 (NF1) gene are predominantly of maternal origin and commonly associated with a learning disability, dysmorphic features and developmental delay. Hum Genet 1998;102:591-7.