Eruptive Neurofibromas in Pregnancy

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Abstract

Neurofibromatosis type 1 is the most common inherited nervous system disorder affecting 1 in 3500 live births. Cutaneous neurofibromas, the most characteristic feature of the disease, begin to appear in adolescence and continue throughout adulthood. Although neurofibromas have been noted to increase in size or number during pregnancy, there have been very few reports of eruption of a large number of lesions during this period. We report a case of a 24-year-old Nigerian woman of 32-week gestation who presented with a history of sudden eruption of neurofibromas during the current pregnancy and the previous one 3 years earlier. We discuss how hormones and growth factors contribute to the increase in numbers of neurofibromas during pregnancy, which is occasionally severe, as in our case, and the complications which may arise in the mother and fetus.

Keywords: Eruptive neurofibromas, neurofibromas, neurofibromatosis type 1, pregnancy

Résumé

La neurofibromatose de type 1 est le trouble du système nerveux héréditaire le plus répandu, touchant 1 naissance sur 3 500 naissances vivantes. Les neurofibromes cutanés, la caractéristique la plus caractéristique de la maladie, commencent à apparaître à l’adolescence et se poursuivent à l’âge adulte. Bien que l’on ait noté une augmentation de la taille ou du nombre des neurofibromes au cours de la grossesse, très peu de cas d’éruption d’un grand nombre de lésions aient été rapportés au cours de cette période. Nous rapportons le cas d’une femme nigérienne de 24 semaines de gestation nigérienne présentant des antécédents d’éruption soudaine de neurofibromes au cours de la grossesse en cours et la précédente trois ans plus tôt. Nous discutons de la manière dont les hormones et les facteurs de croissance contribuent à l’augmentation du nombre de neurofibromes pendant la grossesse, parfois sévère, comme dans notre cas, ainsi que des complications pouvant survenir chez la mère et le fœtus.

Mots-clés: Neurofibromes éruptifs, neurofibromes, neurofibromatose de type 1, grossesse

INTRODUCTION

Neurofibromatosis type 1 (NF1) (Von Recklinghausen’s disease) – an autosomal dominantly inherited disorder – is the most common inherited nervous system disease affecting 1 in 3500 live births.[1] The most characteristic feature of NF1 is cutaneous neurofibromas which begin to appear in adolescence in most patients.[1] Other cutaneous manifestations are café au lait macules, axillary freckling, and plexiform neurofibromas. NF1 may also manifest with ocular, skeletal, central nervous system, neuropsychiatric, cardiovascular, and cerebrovascular abnormalities. Neurofibromas have been noted to increase in size or number in up to 82% of pregnancies,[2] and in rare cases, may appear in large numbers at the same time (eruptive neurofibromas).[3,4] We describe a young Nigerian woman who developed large numbers of neurofibromas during both of her pregnancies and also discuss the likely cause of this increase and highlight complications which may arise in the mother and fetus. We hope this adds to the literature on the subject.

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CASE REPORT

A 24-year-old Nigerian woman, at 32 weeks of gestation, presented to the skin clinic with a large number of soft skin lesions on her chest, back, and arms. She reported that the lesions appeared in large numbers during the first trimester of her first pregnancy 3 years earlier and continued to erupt and increase in size throughout the second and third trimester of that pregnancy and throughout the current pregnancy. The lesions were itchy and occasionally painful. She reported that far fewer lesions developed in the interval between the two pregnancies. She had had multiple dark spots on her chest, abdomen, back, and arms throughout her childhood and adolescence. There was no family history of a similar disorder. Her first pregnancy was unremarkable, and she delivered a normal baby girl. On examination, she had a large number of slightly dark, soft papules and occasional nodules of various sizes, from barely perceptible papules to pedunculated nodules, on her back [Figure 1] and chest and upper abdomen [Figure 2]. In addition, she had innumerable café au lait macules of various sizes on her back, chest, and abdomen [Figure 3], and multiple freckles on the inner aspect of her upper arms but no plexiform neurofibromas. She had mild scoliosis but had no Lisch nodules on eye examination. Cardiovascular, neurologic, and other system examinations and abdominal ultrasonography were normal. We did not perform a computed tomography scan of any organ as it was not affordable. We made a diagnosis of NF1 based on the clinical findings and histology of an excised papule, which was consistent with neurofibroma.

DISCUSSION

Although neurofibromas have been noted to increase in size or numbers in pregnancy in patients with NF1,[3] reports of eruptive neurofibromas in pregnancy are rare.[3,4] Roth et al.[9] have excellently reviewed the hormonal changes that are considered responsible for the increase in number and size of neurofibromas in pregnancies. There is a progressive increase in 17 β-estradiol (E2), progesterone (P4), and testosterone blood levels throughout normal pregnancy which fall to prepregnancy levels within 3 days after delivery.[5] 17 β-estradiol is the most potent effector hormone in pregnancy and has proliferative effect on estrogen-responsive tumor cells.[5] Progesterone, modified to E2, is involved in cell differentiation and modulation of E2 proliferative effects, and both E2 and P4 exert their proliferative effects through induction of angiogenesis.[5] Fishbein et al.[6] using immunochemistry and real-time PCR, have shown that E2, P4, and androgen receptors are differentially expressed in primary neurofibromas and suggest that these steroid hormones may directly initiate neurofibroma formation or progression. 2-methoxyestradiol (2ME2) is a naturally occurring E2 metabolite whose levels in blood also rise during pregnancy, and it appears to prevent hyperproliferation of cells; it has no estrogenic effects but has strong antitumorigenic effects by inhibiting angiogenesis and apoptosis.[7] Roth et al. have postulated that levels of 2ME2 in pregnant women with NF1 may be low, or more likely, cell receptors for 2MES may be lacking in neurofibroma cells which allow unchecked E2 and
P4 promotion of proliferation and growths of neurofibromas in these patients.\(^7\) It is possible that patients with eruptive neurofibromas, such as ours, may express a larger number of steroid receptors in their lesions or have far more profound changes in 2ME2 levels or effect than other pregnant NF1 patients. However, we did not have resources to test this theory. Growth factors, similar to steroid hormones, play a crucial role in the establishment and maintenance of pregnancy and may have a role in the increase in size and numbers of neurofibromas in pregnancy and in puberty. Mashour et al.\(^8\) have shown that growth factors such as midkine and stem cell factor, whose levels are substantially increased even in the serum of nonpregnant NF1 patients than controls, had a more profound effect on proliferation of human neurofibroma-derived primary Schwann cells and endothelial cells than serum from normal controls. Kitano et al.\(^9\) have demonstrated that epidermal growth factor, transforming growth factor alpha, and fibroblast growth factor-induced proliferation of Schwann cells derived from neurofibromas occur at very low levels. This may also play a role in the increase in numbers and size of neurofibromas seen in pregnant patients.

Cardiovascular and cerebrovascular diseases resulting from vasculopathy, a well-known complication of NF1,\(^10\) often first manifest in pregnancy in young patients with NF1; it is likely to be worse in patients with eruptive neurofibromas and may have adverse maternal and fetal outcomes. Terry et al.,\(^10\) in a large study involving 1553 pregnancies in which NF1 diagnosis was also present, found that compared to a control group of pregnant women who did not have NF1, NF1 patients were significantly more likely to develop gestational hypertension, preeclampsia, intrauterine growth retardation, cerebrovascular disease, preterm labor, and cesarean delivery. It is important for clinicians caring for these patients to be aware of these complications and take necessary measures, including genetic counseling, to mitigate and prevent them.

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Conflicts of interest
There are no conflicts of interest.

References
1. Boyd KP, Korf BR, Theos A. Neurofibromatosis type 1. J Am Acad Dermatol 2009;61:1-4.
2. Dugoff L, Sujansky E. Neurofibromatosis type 1 and pregnancy. Am J Med Genet 1996;66:7-10.
3. Xiong M, Gilchrest BA, Obayan OK. Eruptive neurofibromas in pregnancy. JAAD Case Rep 2015;1:23-4.
4. Alonso A, Dauden E, Harnandeza A, Ballester M, Fraga I, García-Diez A. Eruptive neurofibromas during pregnancy. Actas Dermosifiliogr 2004;95:519-21.
5. Roth TM, Petty EM, Barald KF. The role of steroid hormones in the NF1 phenotype: Focus on pregnancy. Am J Med Genet A 2008;146A: 1624-33.
6. Fishbein L, Zhang X, Fisher LB, Li H, Campbell-Thompson M, Yachnis A, et al. In vitro studies of steroid hormones in neurofibromatosis 1 tumors and Schwann cells. Mol Carcinog 2007;46:512-23.
7. Roth TM, Ramamurthy P, Muir D, Wallace MR, Zhu Y, Chang L, et al. Influence of hormones and hormone metabolites on the growth of Schwann cells derived from embryonic stem cells and on tumor cell lines expressing variable levels of neurofibromin. Dev Dyn 2008;237:513-24.
8. Mashour GA, Driever PH, Hartmann M, Drissel SN, Zhang T, Scharf B, et al. Circulating growth factor levels are associated with tumorigenesis in neurofibromatosis type 1. Clin Cancer Res 2004;10:5677-83.
9. Kitano Y, Okamoto E, Saito K, Okano Y. Effects of several growth factors on cultured neurofibroma cells. J Dermatol Sci 1992;2:137-44.
10. Terry AR, Barker FG 2nd, Leffert L, Bateman BT, Souter J, Plotkin SR. Neurofibromatosis type 1 and pregnancy complications: A population-based study. Am J Obstet Gynecol 2013;209:46.e1-8.