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Can isotretinoin be used in treating multiple neurofibromas thanks to its apoptotic effect?

Mine Müjde KUŞ, Perihan ÖZTÜRK

Department of Dermatology, Faculty of Medicine, Kahramanmaraş Sütçü İmam University Onikisubat\ Kahramanmaraş, Turkey.

Abstract

The most common benign tumor of the peripheral nerve sheath is neurofibromas. The only known curative treatment is total surgical excision. In neurofibromatosis patients with multiple cutaneous neurofibromas, it is not possible to treat all neurofibromas with surgical excision. We happened on a case of neurofibromatosis type-1, whose neurofibromas shrank while using isotretinoin for the treatment of excessively oily skin and postadolescent acne. We think that isotretinoin executes this effect through its apoptotic mechanism of action.

Keywords: Neurofibroma, neurofibromatosis, isotretinoin, apoptosis, treatment

INTRODUCTİON

The most common benign tumor of the peripheral nerve sheath is neurofibromas. They emerge from the connective tissue of the endoneurium and peripheral nerve sheath. It is formed by fibroblasts, Schwann cells, perineural cells, and mast cells within the myxoid structure. Cutaneous neurofibromas are mostly seen as soft, skin-colored papules or small subcutaneous nodules.[1] Neurofibroma is of three types: localized, diffuse, and plexiform. While approximately 90% of neurofibromas emerge sporadically, the remaining cases emerge concerning neurofibromatosis type 1 or 2. The plexiform type is pathognomonic for neurofibromatosis type 1. Neurofibromas have an extremely low risk of malignant transformation. But plexiform neurofibromas have a high risk of malignant transformation.[2,3] The treatment method that is accepted to be effective in treating cutaneous neurofibromas is total surgical excision. Currently, there is no approved alternative therapy for the treatment and prevention of cutaneous neurofibromas.[4] Tried Interferon-alpha in the treatment of plexiform neurofibroma, but differing results were obtained.[5] The MEK inhibitor Selumetinib is the first therapeutic agent lately confirmed by the FDA for the treatment of inoperable plexiform neurofibroma linked with neurofibromatosis type-1.[6]

The most successful drug in treating severe acne is currently oral isotretinoin (13-cis retinoic acid). It shows its effect in acne treatment by causing sebocyte apoptosis. Isotretinoin induces the expression of apoptotic protein tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL), insulin-like growth factor-binding protein-3, and neutrophil gelatinase-associated lipocalin, which activates apoptosis and cell cycle inhibitors. The desired and undesirable effects of oral isotretinoin treatment are related to its apoptotic effect.[7]

We happened in a case of neurofibromatosis type-1, whose cutaneous neurofibromas shrunk while using isotretinoin to treat excessive fat on the skin and post-adolescent acne. We presented the case to draw attention to the fact that isotretinoin can be used in treating multiple neurofibromas thanks to its apoptotic action mechanisms.

CASE REPORT

A 43-year-old female patient complained of excessive facial oiliness, enlarged pores, and acne. She was previously diagnosed with neurofibromatosis type-1 by us. She had multiple neurofibromas, cafe au lait spots, axillary freckling, and diffuse hyperpigmentation all over the body (Figure 1). Her father and older brother also had neurofibromatosis type-1. On examination, increased sebum on the skin, open comedones,

Address correspondence to: Mine Müjde KUŞ, MD, Kahramanmaraş Sütçü İmam University Faculty of Medicine, Department of Dermatology, West Ring Road Boulevard 251/A, 46050 Onikisubat\Kahramanmaraş, Turkey. Email: mmujde_ozdemir@hotmail.com

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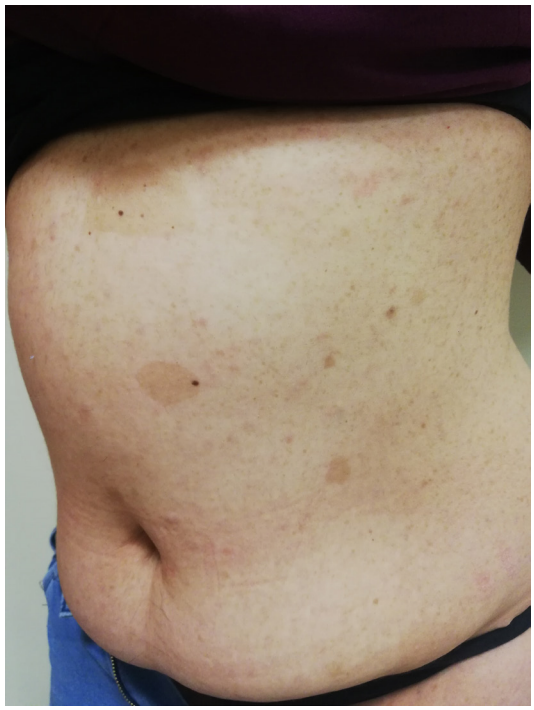

Figure 1. Cafe au lait spots, neurofibromas, and diffuse hyperpigmentation on the patient's abdominal skin

and papulopustular acne were observed. It was learned that she did not benefit from the topical treatments she had used before. Oral isotretinoin 30mg/day (0.5mg/kg/day) treatment was planned because there was no response to other treatments. Laboratory findings were normal. She used 30mg/day of oral isotretinoin regularly for one month. At the follow-up one month later, the patient stated that his neurofibromas had shrunk. Because of this expression of the patient, neurofibromas were photographed. At the 2nd month follow-up, neurofibromas were re-evaluated, and the lesions decreased (Figure 2A-B and Figure 3A-B).

After the 2nd month of the treatment, the patient stopped oral isotretinoin because she was bothered by the drug-induced dryness and the improvement in her skin was sufficient for her. In her control, two months after stopping the drug, there was no change in the size and number of neurofibromas, but the complaint of oily skin returned.

DİSCUSSİON

Since most neurofibromas are sporadic and localized, they can be treated with surgical excision. However, in neurofibromatosis patients, neurofibromas can be seen all over the body, including the mucosal surfaces, and can be in hundreds. Therefore, it is not possible to treat all of them with surgical excision. They usually do not cause any complaints other than cosmetic problems. In large numbers, it can cause itching and threaten organ function due to its location. There is a need for a treatment alternative other than surgery for patients with multiple lesions, and new tumors continue to emerge. Different results have been obtained from treatment with interferon-alpha, apart from surgical treatment in the treatment of plexiform neurofibroma.[4,5] The first

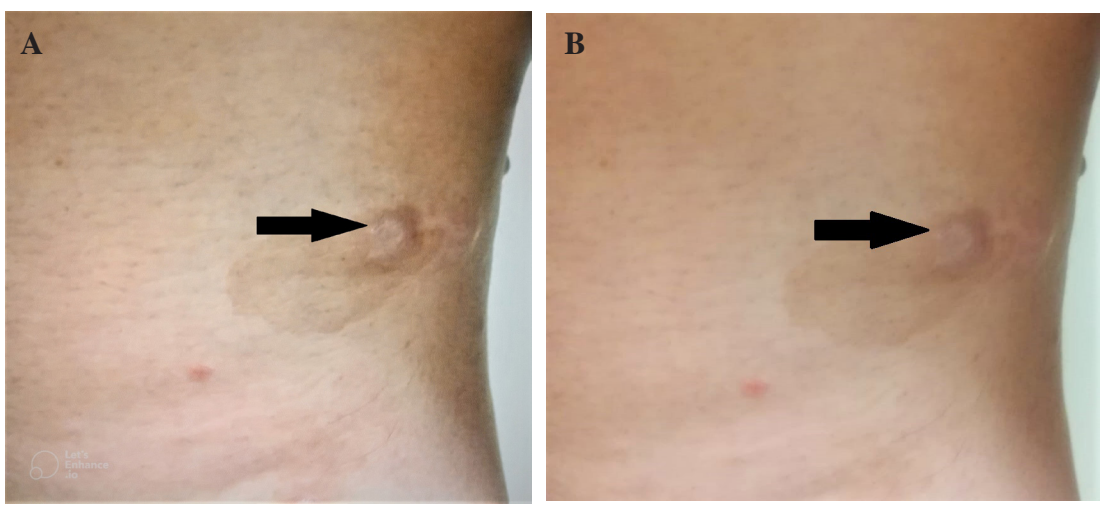

Figure 2. A. Images at the end of the first month of the isotretinoin treatment of a neurofibroma in the same localizatıon as the cafe-au-lait spot and two subsantimetric neurofibromas in the inferior in the posteromedial of the left thigh. B. Images at the end of the second month of the isotretinoin treatment of a neurofibroma in the same localizatıon as the cafe-au-lait spot and two subsantimetric neurofibromas in the inferior in the posteromedial of the left thigh.

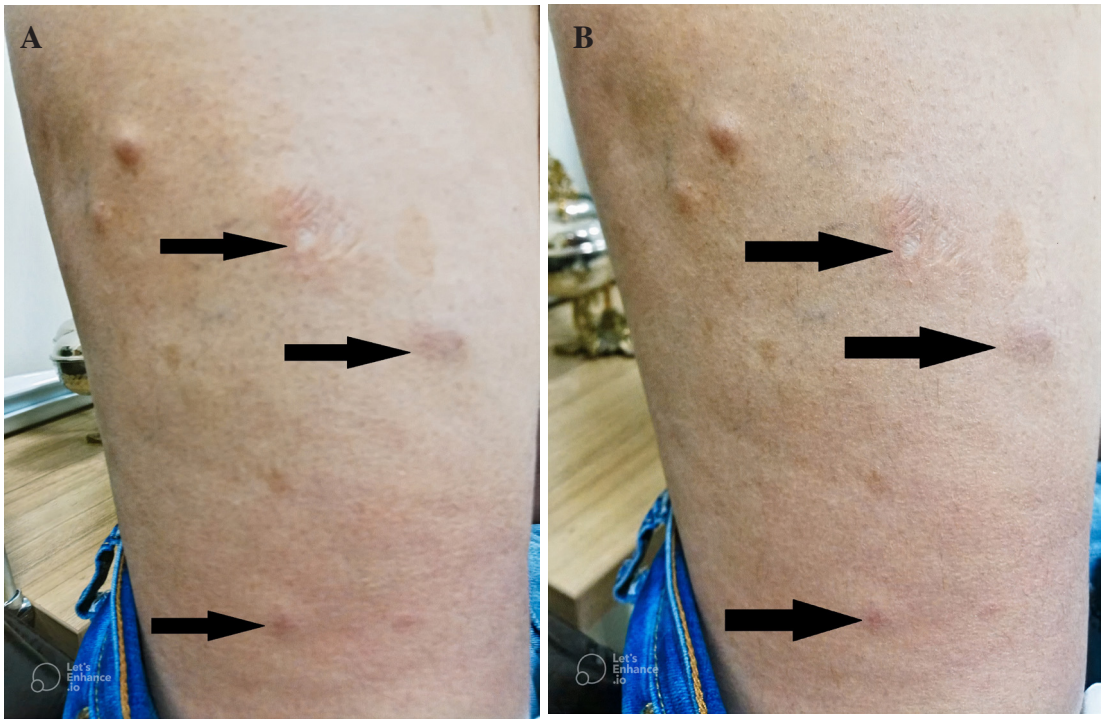

Figure 3. A. Images at the end of the first month of the isotretinoin treatment of two neurofibromas in the anterolateral of the right leg. B. Images at the end of the second month of the isotretinoin treatment of two neurofibromas in the anterolateral of the right leg.

agent to receive FDA approval for the treatment of plexiform neurofibroma was selumetinib. In the Phase II study, a more than 20% reduction in the size of plexiform neurofibroma was detected in 70% of patients. It caused dose-limiting toxicity in 38%.[8] Results of the phase II SPRINT trial led to FDA confirmation of selumetinib for inoperable plexiform neurofibroma in pediatric patients. Studies on the use of selumetinib in treating cutaneous neurofibromas are ongoing.[6]

Oral isotretinoin carries out its sebum suppressive effect by inducing apoptosis of sebocytes.[9] After isotretinoin isomerized to all-trans retinoic acid (ATRA), ATRA binds to the retinoic acid receptor (RAR), and the transcription factor FoxO3a is upregulated. Expression of the tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL) and FoxO1 are induced by FoxO3 at the promoter level. The caspase cascade activated by TRAIL leads to apoptosis. Cell cycle inhibitors p21 and p27 up-regulated by FoxO1 lead to cell cycle arrest (Figure 4).[7]

Isotretinoin is used to treat various malignancies due to its apoptotic effects and mediating effects on cell cycle arrest (Neuroblastoma, Acute promyelocytic leukemia, Adult T-cell lymphoma). It is also applied to those with genodermatoses to lower their risk of skin cancer (xeroderma pigmentosum and nevoid basal cell carcinoma syndrome).[10-13]

Constitutively expressed in most human tissues, TRAIL causes relatively less damage in healthy cells than in abnormal cells while inducing apoptosis in tumor cell lines.[7,14]

Neurofibromatosis type-1 is a common autosomal dominant disease caused by mutations in the neurofibromatosis type 1 tumor suppressor (NF1) gene. Neurofibromas occur due to the inactivating somatic mutation in the NF1 allele. In neurofibromatosis type-1 patients, neurofibromas often emerge during adolescence, and their number progressively increases.[4,15] We detected a shrinkage in neurofibromas with oral isotretinoin treatment when using oral isotretinoin due to the acne and increased sebum in our patient with neurofibromatosis type-1. Neurofibromas occur due to abnormal proliferation in perineural cells since the tumor suppressor function in the mutated NF1 gene in neurofibromatosis patients cannot be fulfilled.[4,15] Conversely, isotretinoin induces the expression of TRAIL and FoxO1. TRAIL causes apoptosis by activating the caspase cascade. FoxO1 upregulates the cell cycle inhibitors p21 and p27, mediating cell cycle arrest.[7] We think that

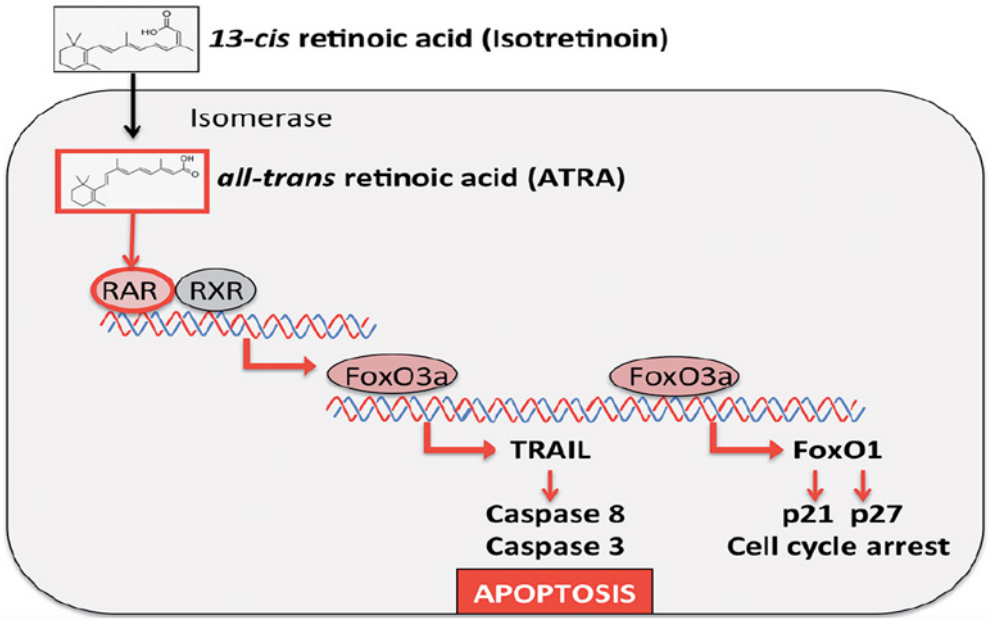

Figure. 4. The hypothesis of apoptosis signaling pathways explaining the desired and undesirable effects of isotretinoin. After isotretinoin isomerized to all-trans retinoic acid (ATRA), ATRA binds to the retinoic acid receptor (RAR), and the transcription factor FoxO3a is upregulated. Expression of the tumor necrosis factor-associated apoptosis-inducing ligand (TRAIL) and FoxO1 are induced by FoxO3 at the promoter level. The caspase cascade activated by TRAIL leads to apoptosis. Cell cycle inhibitors p21 and p27 upregulated by FoxO1 lead to cell cycle arrest. (With permission of Bodo C Melnik)[7]

isotretinoin may cause a significant reduction in the size of neurofibromas by inducing apoptosis and arresting the cell cycle. We recommend that prospective studies be conducted on the use of isotretinoin for the treatment and prevention formation of neurofibromas.

DISCLOSURE

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REFERENCES

1. Ferner RE, O'Doherty MJ. Neurofibroma and schwannoma. *Curr Opin Neurol* 2002;15(6):679-84. doi: 10.1097/01.wco.0000044763.39452.aa.
2. Skovronsky DM, Oberholtzer JC. Pathologic classification of peripheral nerve tumors. *Neurosurg Clin N Am* 2004;15(2):157-66. doi: 10.1016/j.nec.2004.02.005.
3. Lassmann H, Jurecka W, Lassmann G, Gebhart W, Matras H, Watzek G. Different types of benign nerve sheath tumors. Light microscopy, electron microscopy and autoradiography. *Virchows Arch A Pathol Anat Histol* 1977;375(3):197-210. doi: 10.1007/BF01102988.
4. Allaway RJ, Gosline SJC, La Rosa S, *et al*. Cutaneous neurofibromas in the genomics era: current understanding and open questions. *Br J Cancer* 2018;118(12):1539-48. doi: 10.1038/s41416-018-0073-2.
5. Kebudi R, Cakir FB, Gorgun O. Interferon-α for unresectable progressive and symptomatic plexiform neurofibromas. *J Pediatr Hematol Oncol* 2013;35(3):e115-e117. doi: 10.1097/MPH.0b013e318270cd24.
6. Galvin R, Watson AL, Largaespada DA, Ratner N, Osum S, Moertel CL. Neurofibromatosis in the era of precision medicine: Development of MEK inhibitors and recent successes with selumetinib. *Curr Oncol Rep* 2021;23(4):45. doi: 10.1007/s11912-021-01032-y.
7. Melnik BC. Apoptosis may explain the pharmacological mode of action and adverse effects of isotretinoin, including teratogenicity. *Acta Derm Venereol* 2017;97(2):173-81. doi: 10.2340/00015555-2535.
8. Gross AM, Wolters PL, Dombi E, *et al.* Selumetinib in children with inoperable plexiform neurofibromas [published correction appears in *N Engl J Med* 2020 24;383(13):1290]. *N Engl J Med* 2020;382(15):1430-42. doi: 10.1056/NEJMoa1912735.
9. Nelson AM, Gilliland KL, Cong Z, Thiboutot DM. 13-cis Retinoic acid induces apoptosis and cell cycle arrest in human SEB-1 sebocytes. *J Invest Dermatol* 2006;126(10):2178-89. doi: 10.1038/sj.jid.5700289.
10. Bayeva N, Coll E, Piskareva O. Differentiating neuroblastoma: A systematic review of the retinoic acid, its derivatives, and synergistic interactions. *J Pers Med* 2021;11(3):211. doi: 10.3390/jpm11030211.

11. Jiménez-Lara AM, Clarke N, Altucci L, Gronemeyer H. Retinoic-acid-induced apoptosis in leukemia cells. *Trends Mol Med* 2004;10(10):508-15. doi: 10.1016/j.molmed.2004.08.006.
12. Maeda Y, Miyatake J, Sono H, *et al*. 13-cis retinoic acid inhibits growth of adult T cell leukemia cells and causes apoptosis; possible new indication for retinoid therapy. *Intern Med* 1996;35(3):180-4. doi: 10.2169/internalmedicine.35.180.
13. Bettoli V, Zauli S, Virgili A. Retinoids in the chemoprevention of non-melanoma skin cancers: why, when and how. *J Dermatolog Treat* 2013;24(3):235-7. doi: 10.3109/09546634.2012.746634.
14. Kelhälä HL, Fyhrquist N, Palatsi R, *et al*. Isotretinoin treatment reduces acne lesions but not directly lesional acne inflammation. *Exp Dermatol* 2016;25(6):477-8. doi: 10.1111/exd.12971.
15. Tucker T, Riccardi VM, Brown C, *et al*. S100B and neurofibromin immunostaining and X-inactivation patterns of laser-microdissected cells indicate a multicellular origin of some NF1-associated neurofibromas. *J Neurosci Res* 2011;89(9):1451-60. doi: 10.1002/jnr.22654.