ONLINE EXCLUSIVE

Neurofibromatosis with multiple bilateral choroidal nevi and literature review

BY MEHRU-NISAH HANIF, SYED RAZA ALI ZAIDI AND NAUSHEEN HAYAT

The aim is to present a case of neurofibromatosis type-1 (NF-1), also known as von Recklinghausen disease, who presented with bilateral multiple choroidal nodular nevi following chemotherapy and mastectomy for breast cancer. Neurofibromatosis type-1 presents as a wide range of skin, bone, nervous system, and soft tissue abnormalities. The most common ocular / periocular manifestations of NF-1 are optic nerve glioma, sphenoid meningioma, eyelid neurofibroma and café-au-lait spots. This also exhibits pigmentary tissue involvement such as iris and choroid. Interestingly, NF-1 has an autosomal dominant mode of transmission but with variable expression and complete penetrance. Notably, there is high suspicion of both benign and malignant tumours.

Revised diagnostic criteria for NF-1, 2021 [1]

- Six or more café-au-lait macules over 5mm in greatest diameter in pre-pubertal individuals and over 15mm in greatest diameter in post-pubertal individuals
- Freckling in the axillary or inguinal region
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Optic pathway glioma
- Two or more iris Lisch nodules identified by slit-lamp examination or two or more choroidal abnormalities – defined as bright, patchy nodules imaged by optical coherence tomography (OCT) / near-infrared reflectance (NIR) imaging
- A distinctive osseous lesion such as sphenoid dysplasia
- A heterozygous pathogenic NF-1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells.

Case report

A 40-year-old lady, asymptomatic, who is a known case of NF-1, was urgently referred by optician to the eye clinic with new onset unusual bilateral choroidal lesions. There was high suspicion of choroidal metastasis given the history of breast cancer which was recently treated with surgery and chemotherapy.

In the past, she has had multiple removals of subcutaneous tumours with subsequent diagnosis of neurofibromas, confirmed on histopathology examination. She was diagnosed as grade 3 invasive breast cancer with metaplastic features when she had biopsy of left-sided lump in 2021. She had left mastectomy and sentinel lymph node biopsy in March 2022, preceded by chemotherapy. There was no metastasis found at that time through blood tests, MRI brain, x-rays or bone scans. She has longstanding multiple iris Lisch nodules in both eyes. Her bilateral choroidal lesions were picked up by the optician as an incidental finding. This was an unusual presentation of bilateral multiple symmetrical nevi.

On ophthalmological examination, her best corrected visual acuity was 6/6 in both eyes. Her bilateral iris Lisch nodules remained stable on comparison to old photographs. Notably, there were multiple choroidal freckling without lipofuscin or drusen present in the posterior pole (Figures 1 and 2 are the colour fundus images of well-defined multiple choroidal nevi; green arrows indicate the choroidal nodules), which was not reported during previous eye examination. On OCT scan,

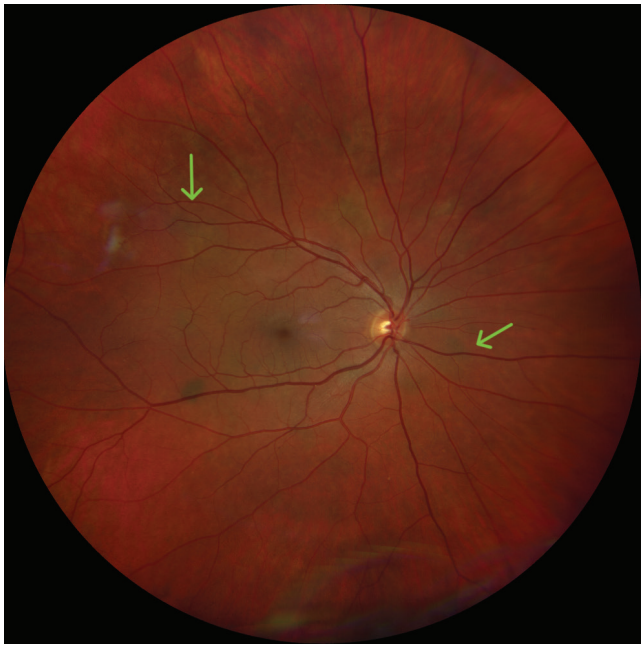

Figure 1: Right eye.

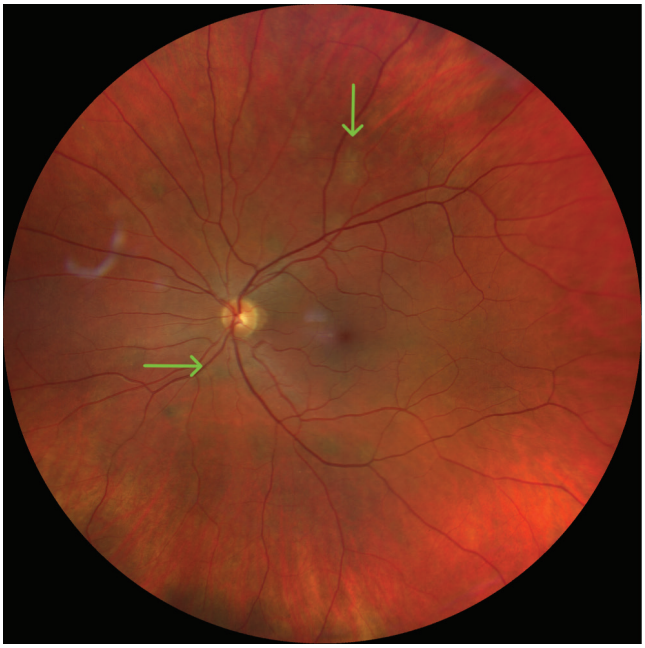

Figure 2: Left eye.

> “While chemotherapy is known to induce a wide range of systemic side effects, its impact on the development or progression of benign ocular lesions in the population remains unclear.”

there was no intraretinal or subretinal fluid present. Retinal pigment epithelium was intact and there was no retinal detachment. Fundus autofluorescence showed very mild hypoflourescence over the same areas of nevi bilaterally with absence of microvascular abnormalities. Visual fields were full and remained within normal limits.

She was referred to the ocular oncology centre at Liverpool in October 2022 for further investigations due to high suspicion of malignancy. Then, she was referred back to us as these lesions found to be benign in nature due to absence of sinister features. She is under our care for annual monitoring and there is no evidence of choroidal metastasis so far.

Conclusion

The authors present this case because new onset clinically significant benign choroidal naevi in a known case of NF-1 after chemotherapy and mastectomy for breast cancer has never been reported before. There were no retinal microvascular abnormalities noted on OCT in this case. She only had ocular features of iris Lisch nodules previously on regular follow-ups, which supports the revised diagnostic criteria of NF-1. There was no ocular malignancy seen.

Patient perspective

She was reassured that there was no ocular malignancy seen and no ocular treatment warranted.

Discussion

While the association between NF-1 and various ocular manifestations, including Lisch nodules and choroidal abnormalities, is well-established, the emergence of these lesions post-chemotherapy warrants further discussion.

As highlighted in the case, choroidal abnormalities, particularly occult choroidal and retinal lesions, are quite common in NF-1, which is also defined in recently updated NF-1 diagnostic criteria released in 2021. It is crucial to differentiate these lesions from other conditions that can mimic the appearance of choroidal abnormalities in NF-1. One such example is Cornflake Nevoid lesions, as described by Papasavvas, et al. [2]. This emphasises the importance of careful, differential diagnosis using multimodal imaging techniques.

The existing literature provides limited data on the direct correlation between chemotherapy and the development of choroidal nevi in NF-1 patients. While chemotherapy is known to induce a wide range of systemic side effects, its impact on the development or progression of benign ocular lesions in the population remains unclear.

Tadini, et al. explored the diagnostic criteria for NF-1, highlighting the prevalence of iris and choroidal abnormalities [3]. However, their study did not specifically address the influence of chemotherapy on these manifestations. Similarly, Ferner, et al. provided comprehensive guidelines for NF-1 management, emphasising the importance of ophthalmologic surveillance [4]. Yet, they did not delve into the potential implications of chemotherapy on ocular findings.

This case highlights the development of new symmetrical and bilateral choroidal lesions not previously observed in the patient, raising a strong suspicion of malignancy due to her background of multiple systemic tumours. This emphasises the critical need for regular ophthalmic examinations with multimodal imaging in these patients.

The timing of the appearance of choroidal nevi in our patient, shortly after chemotherapy, raises the possibility of a causal relationship. It is plausible that chemotherapy, with its known effects on cell growth and proliferation, might trigger the development of these lesions in individuals genetically predisposed to NF-1.

Alternatively, the lesions might have emerged as part of the natural history of NF-1, independent of the chemotherapy. Recently, there have been discussions about pigmented choroidal abnormalities with frequency up to 100% identified with near-infrared reflectance / OCT as a new ocular sign in NF-1 due to easy access to non-invasive multimodal imaging techniques [5].

This case underscores the importance of comprehensive ophthalmologic evaluation and long-term monitoring for individuals with NF-1, particularly those undergoing chemotherapy. Early detection and characterisation of any new ocular lesions are essential to ensure appropriate management and prevent potential complications.

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AUTHORS

Mehru-Nisah Hanif, MBBS, FRCSEd, FRCOphth, FCPS,
Consultant Ophthalmologist, Abergele Hospital, Betsi Cadwaladr University Health Board, UK.

Syed Raza Ali Zaidi, MRCS, FRCS,
Consultant Ophthalmologist and Vitreoretinal Surgeon, James Paget University Hospital, UK.

Nausheen Hayat, MBBS, MRCOphth, FCPS,
Oculoplastic Fellow, Royal London Hospital, UK.

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