EJCRIM
European Journal
of Case Reports
in Internal Medicine

UNILATERAL YASUNARI NODULE-LIKE APPEARANCE IN A PATIENT WITHOUT NEUROFIBROMATOSIS TYPE 1

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Received: 09/12/2025
Accepted: 15/12/2025
Published: 12/01/2026

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.
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How to cite this article: Ali H, Ahmadova N, Fatihoglu OU, Kocabey M, Caglayan AO, Saatci AO. Unilateral Yasunari nodule-like appearance in a patient without neurofibromatosis type 1. *EJCRIM* 2026;**13**:doi:10.12890/2026_006071

ABSTRACT

Introduction: Yasunari nodules are choroidal lesions characterized by bright, poorly demarcated multiple lesions detected through near-infrared reflectance imaging and are considered diagnostic for neurofibromatosis type 1 (NF1). We report a case of unilateral Yasunari-like nodules in a patient without clinical or genetic evidence of NF1.

Case description: A 53-year-old male presented with a 7-day history of floaters in both eyes. Best-corrected visual acuity was 20/20 in the right eye and 20/25 in the left eye. Slit-lamp examination revealed bilateral multiple iris nevi. Both fundi appeared normal on colour photography. The right infrared image demonstrated multiple bright, relatively well-defined areas suggesting Yasunari nodules, whereas the left infrared image was normal. Green and blue autofluorescent images were unremarkable bilaterally. Spectral domain optical coherence tomography revealed poorly demarcated hyperreflective choroidal nodule-like changes in the right eye only. Physical examination revealed no signs of NF1. Next-generation deoxyribonucleic acid sequencing of blood and skin specimens was negative for NF1.

Discussion: This is the second reported case of unilateral Yasunari-like nodules in a patient without NF1. Despite extensive clinical and genetic evaluation, including testing for somatic mosaicism, all results were negative for NF1. The lesions were considered benign incidental findings and monitored conservatively.

Conclusion: Although infrequent, lesions resembling Yasunari nodules may be observed in patients without NF1. Clinicians should be aware of this possibility when encountering similar imaging findings.

KEYWORDS

Choroid, infrared image, neurofibromatosis type 1, NF1, Yasunari nodules

LEARNING POINTS

- Clinicians should be aware of the fact that, although the presence of choroidal nodules (Yasunari nodules) is pathognomonic for the diagnosis of neurofibromatosis type I, similar choroidal appearances may occasionally be observed in normal eyes on infrared imaging.

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INTRODUCTION

Yasunari nodules are choroidal lesions characterized by irregular, poorly demarcated, brightly appearing multiple lesions, predominantly detected through near-infrared (IR) imaging. They tend to be bilateral and are considered among the defining signs of neurofibromatosis type 1 (NF1)[1,2]. Given its high specificity and sensitivity for NF1, Yasunari nodules were incorporated as an ocular diagnostic criterion for NF1 in the 2021 NF1 International Revised Consensus[2]. de Rivas et al.[1] reported that choroidal nodules are observed in nearly 100% of patients with NF1, excluding only those patients with high myopia. Abdolrahimzadeh et al.[3] delineated two subtypes of choroidal nodules: a round, shiny, well-defined, and easily identifiable type, and a patchy, dull, irregular, and poorly defined type. We describe the presence of multiple, bright, well-defined, and easily recognizable unilateral lesions on infrared reflectance images resembling the Yasunari nodules in a patient with no clinical or genetic evidence of NF1.

CASE DESCRIPTION

We examined a 53-year-old male with a 7-day history of floaters in both eyes. He had well-controlled systemic hypertension, an umbilical hernia, a history of surgeries for papillary thyroid carcinoma (November 2024) and aortic dissection (January 2025), and multiple pulmonary parenchymal nodules that were monitored without intervention by pulmonary medicine. His family history was notable for his father, who succumbed to gastric cancer at the age of 48, and his uncle, who passed away due to a pulmonary malignancy.

On examination, best-corrected visual acuity was 20/20 in the right eye and 20/25 in the left eye. Intraocular pressure was within normal limits in both eyes. Slit-lamp examination disclosed minute iris freckles and a few iris nevi bilaterally. Both posterior poles appeared normal on colour fundus photography (Optos California RGB; Nikon, Dunfermline, Scotland) *(Fig. 1A and B)*. Most notably, the right IR image (Heidelberg Retinal Angiography 2) depicted multiple bright, well-defined, and easily identifiable lesions, suggesting the presence of Yasunari nodules at the posterior pole, whereas the left IR image appeared normal *(Fig. 1C and D)*. The green and blue autofluorescent images of the right fundus depicted a hyperautofluorescent lesion approximately two disk diameters in size, located temporally to the fovea. This lesion was unrelated to the bright multiple lesions observed on the IR image and was presumed to be a choroidal nevus *(Fig. 2A, B and C)*. In contrast, the left autofluorescent images were normal. Enhanced depth spectral domain optical coherence tomography (OCT) (Spectralis OCT®, Heidelberg Engineering, Heidelberg, Germany) revealed poorly demarcated hyperreflective choroidal nodules in the right eye *(Fig. 2D and E)*, whereas the left eye appeared normal. The en face optical coherence tomography of the right eye was nearly normal (Triton, Topcon Inc., Oakland, New Jersey, USA) *(Fig. 2F)*.

In order to confirm or exclude the diagnosis of NF1, we conducted multiple additional investigations. First, total genomic deoxyribonucleic acid (DNA) was isolated from the patient's peripheral blood using the HiPurA® Pre-filled Clinical Multipurpose Nucleic Acid Purification Kit (HiMedia, USA). After obtaining DNA of sufficient quality (50-100 ng/µl concentration and A260/A280: 1.8-2.0 purity), next-generation sequencing was performed. A multigene hereditary cancer panel approach was selected due to the patient's history of thyroid cancer and a family history of gastric cancer. The panel consisted of 35 genes, including *APC*, *ATM*, *BARD1*, *BLM*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK2*, *CTNNB1*, *EPCAM*, *MEN1*, *MLH1*, *MRE11*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PRSS1*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *RB1*, *SLX4*, *SMAD4*, *STK11*, *TP53* and *VHL*. Libraries were

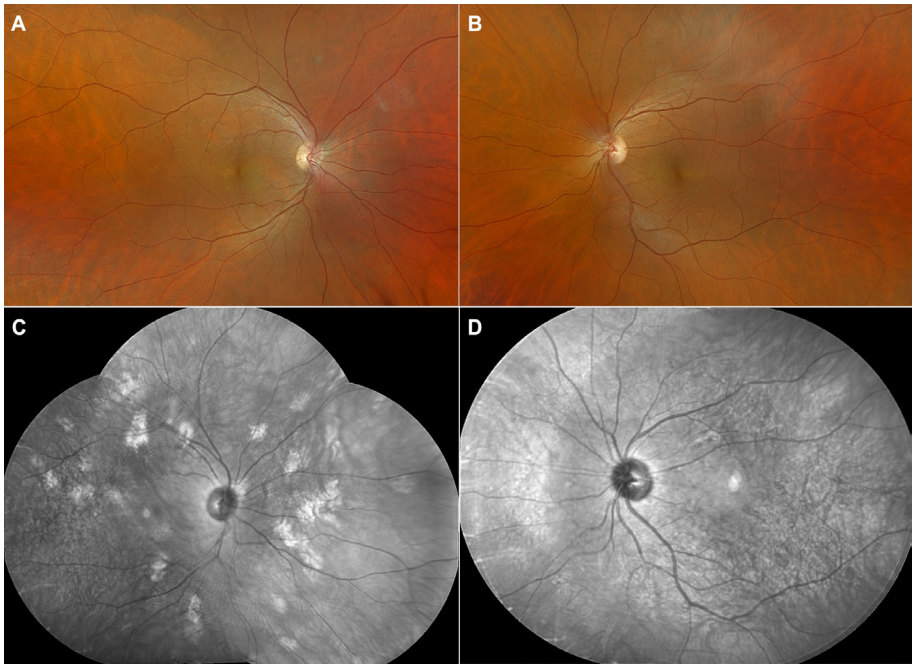


Figure 1. *Normal appearing right and left fundus (A and B). Multiple relatively well-defined scattered hyperreflective, bright lesions at the posterior pole on the right infrared (IR) image (C). The IR image of the left eye appears to be normal (D).*

prepared using the Hereditary Cancer Plus Kit (Celemics, South Korea) according to the manufacturer's protocols. Next-generation sequencing was performed on the NovaSeq platform (Illumina, USA). Bioinformatic analysis, including quality assessment, mapping, alignment, variant calling, and annotation, was carried out with the SEQ software (Genomize, Turkey). For all genes, 100% coverage was obtained at a minimum read depth of 20×. No pathogenic or likely pathogenic variant was detected.

As the patient had unilateral Yasunari-like nodules, we considered the potential diagnosis of mosaic neurofibromatosis and accordingly planned further investigations. Although there were no overt skin lesions indicative of neurofibromatosis, several cutaneous nodules were present. We performed a punch biopsy of one of the larger lesions, which was histologically identified as a fibrovascular lipoma. Genetic testing performed on the skin tissue also yielded a negative result for *NF1* gene. Abdominal magnetic resonance imaging did not reveal any abnormalities aside from a hyperechoic solid lesion in the liver, which was interpreted as a haemangioma, and a few parapelvic cysts. Following the investigations outlined above, we have elected to monitor the Yasunari nodule-like lesions.

DISCUSSION

Choroidal nodules were named after Yasunari, as they were initially identified in all study participants with NF1 in their study[2]. Two or more choroidal nodules have been added as an ocular diagnostic criterion for the diagnosis of NF1 due to their specificity for NF1, serving as an alternative to the Lisch nodules[4]. It is believed that these nodules result from an increase in regional melanocyte count, characterized by oval structures composed of proliferating Schwann cells arranged in concentric rings around the axons[5]. Yasunari nodules are not detectable by biomicroscopy or conventional colour fundus photography. IR imaging utilizing high wavelengths appears to be an optimal modality for evaluating the ocular structures situated beneath the retinal pigment epithelium and functions as an invaluable tool for the visualization of choroid pathologies[6]. Yasunari nodules associated with NF1 can be observed as multiple bright patches exclusively on IR imaging, which is regarded as the gold standard for their detection[7].

The colour fundus photograph, along with green and blue autofluorescent images, was entirely normal in the present case. We designated the unilateral, multiple lesions, observable exclusively through IR imaging, as Yasunari-like lesions. We recently examined 27 patients with NF1, and at least one Yasunari nodule was identified on IR imaging in 52 eyes of these patients[4]. The borders of the lesions were not distinctly demarcated in some patients in that paper, resembling the lesions observed in the right eye of

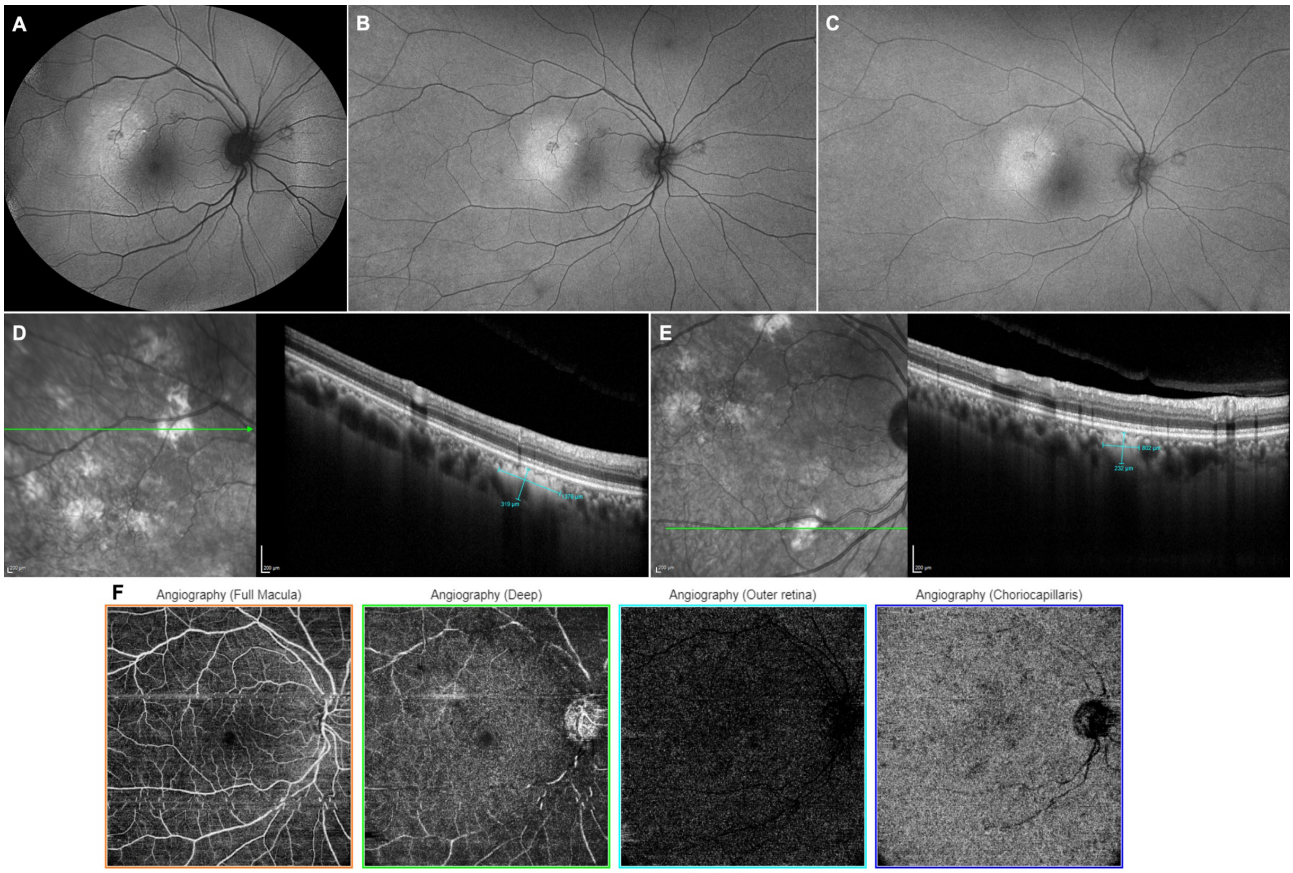


Figure 2. The green (B) and blue autofluorescent (A and C) images reveal a hyperautofluorescent lesion approximately two-disc diameters in size within the posterior pole, which is not related to the choroidal lesions. On enhanced depth imaging optical coherence tomography images of the right eye, choroidal nodules measuring 1376 × 319 µm (D) and 802 × 232 µm (E) are observed as highly reflective lesions in sections passing through high-reflectivity areas on IR reflectance imaging. The en face optical coherence tomography of the right eye was almost normal (F).

the present case. Therefore, we suspected that the patient might have NF1. Although no consistent clinical findings were observed, we conducted a thorough genetic evaluation, which yielded negative results. The hyperautofluorescent area observed on both green and blue autofluorescent images, situated temporally to the fovea, was an innocent bystander, a choroidal nevus.

The only case comparable to ours was documented by Abdolrahimzadeh et al.[7]. They described a 63-year-old male presenting without ocular symptoms who exhibited unilateral hyperreflective areas visible exclusively on IR imaging. Indocyanine green angiography revealed multiple hypocyanescent areas corresponding to those lesions. An extensive systemic workup was negative for NF1, similar to our case. No changes were observed during the 3-year follow-up. They hypothesized that these choroidal alterations could be attributable to somatic mosaicism of NF1 or an as-yet-unrecognized condition; however, genetic analysis for somatic mosaicism was not conducted. In our case, despite conducting numerous supplementary investigations, including detailed genetic analyses, all results were negative. Nevertheless, the possibility of somatic mosaicism cannot be definitively ruled out.

To the best of our knowledge, the present case is the second documented occurrence of Yasunari nodule-like lesions in a patient without NF1. We considered these asymptomatic nodules as benign incidental findings. In light of our observations, clinicians should bear in mind that lesions resembling Yasunari nodules, although infrequent, may be present in patients without NF1.

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