

Solid Tumour Section

Mini Review

Head and Neck: Iris Hamartomas

Hayyam Kiratli

Ocular Oncology Service, Department of Ophthalmology, Hacettepe University School of Medicine, Ankara, Turkey (HK)

Published in Atlas Database: February 2009

Online updated version: <http://AtlasGeneticsOncology.org/Tumors/IrisHamartomaD5100.html>

DOI: 10.4267/2042/44673

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2010 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Note

A hamartoma is defined as a benign tumor or nodular growth that is composed of proliferating mature histologically normal cells that normally reside at the affected tissue. In ophthalmic jargon, iris hamartomas traditionally refer to Lisch nodules which are encountered in patients with neurofibromatosis type 1 (NF1).

Classification

Apart from the Lisch nodules, iris mamillations, iris nevi and melanocytomas must also be considered as hamartomatous benign lesions.

Clinics and pathology

Disease

Lisch nodules

Note

Lisch nodules are dome-shaped gelatinous masses developing on the surface of the iris. Gold-tan to brown in color, they may grow up to 2 mm in diameter and attain variable sizes on the same iris. The presence of Lisch nodules is the most common clinical sign of NF1.

Phenotype / cell stem origin

Lisch nodules are postulated to arise from mast cells, pigmented cells and fibroblast-like cells.

Epidemiology

Lisch nodules are more frequent in post-pubertal NF1 patients evidenced by the finding that only 19% of patients with NF1 below the age of 5 years

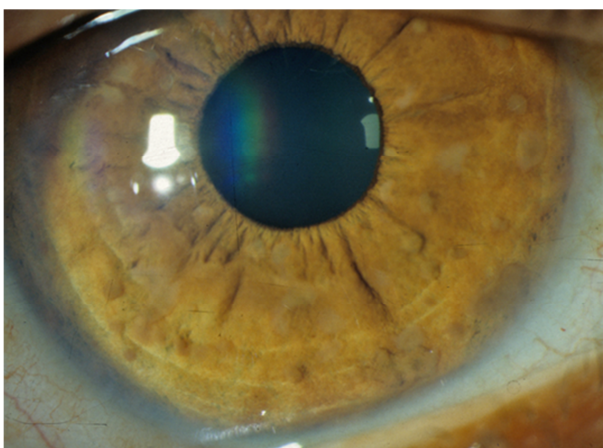
display Lisch nodules whereas this rate rises to 92% in adult NF1 patients. Ninety-three percent of cases are bilaterally affected and an average of 25 nodules can be counted on each iris. Once developed, they remain stable throughout life.

Clinics

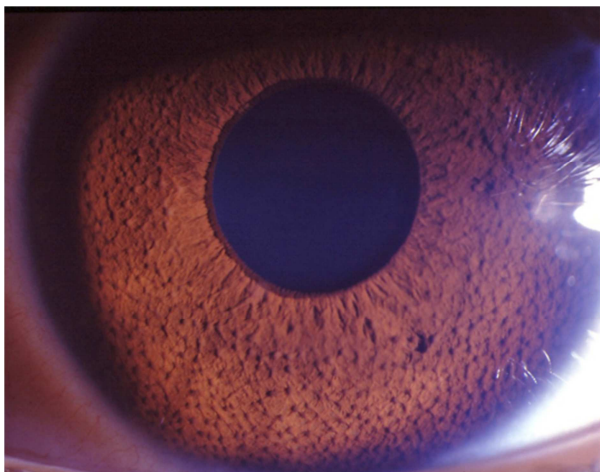
In 80% of eyes, Lisch nodules may be found in the inferior quadrants of the iris and this may be related to greater sun exposure, one of the postulated factors in the development of these benign tumefactions. Lisch nodules are almost always pathognomonic for NF1. However, they may occasionally be seen in some other rare conditions including Watson syndrome and neurofibromatosis type 2. The differential diagnosis of Lisch nodules must include iris mamillations, iridocorneo-endothelial syndrome, Rieger's anomaly or syndrome, iris nevi, melanoma and inflammatory conditions like sarcoidosis, lepra, tuberculosis and syphilis. Differentiating Lisch nodules from iris mamillations may sometimes be particularly important. Iris mamillations are usually unilateral, causing heterochromia iridis and are often associated with ocular melanocytosis. In contrast to Lisch nodules, iris mamillations show the same color as the underlying iris, are regularly spaced over the iris and increase in size as they get closer to the pupillary margin. These eyes should be closely surveyed because of the risk of pigmentary glaucoma which results from excessive pigment accumulation occluding the iridocorneal angle.

Pathology

Histopathologically, Lisch nodules are composed of melanocytes and spindle cells, usually concentrated on the superficial layers of the iris stroma.



Typical light brown-tan colored Lisch nodules on the iris of a patient with neurofibromatosis type 1. The spindle cells are larger than the normal iris melanocytes. Immunohistochemical studies show positive reaction against vimentin, smooth muscle actin and neuron specific enolase.



Multiple, regularly spaced protuberances or "mamillations" on the surface of the iris.

Treatment

Currently there is neither treatment for Lisch nodules nor any necessity to treat these small benign lesions which do not interfere with visual function.

Prognosis

The prognosis is excellent for eyes that contain iris Lisch nodules, unless associated with other ocular lesions including optic nerve gliomas and epiretinal membranes.

Disease

Nevus

Note

This is the most frequent melanocytic lesion involving the iris and mostly localized within the stroma.

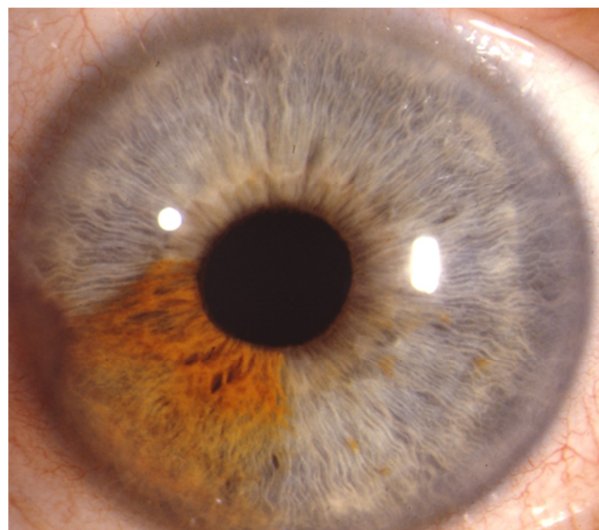
Epidemiology

Iris nevi can be seen in 4-6% of the population, probably more frequently in light irides. Rare in

children, iris nevi become more apparent in puberty and adolescence.

Clinics

Iris nevi can be found on any part of the iris, measuring less than 3 mm in diameter and less than 1 mm in thickness. Most nevi are pigmented but sometimes they may be amelanotic and associated with clear cysts. There is no prominent intralosomal vascularity. On rare occasions an iris nevus may present as small multiple overlapping nodules called as the "tapioca" type. There may be an associated sector cataract. Iridocorneal angle involvement, deformation of the pupillary margin and development of ectopium uvea and minimal growth over time can be observed with iris nevi and do not necessarily imply malignant transformation. Most nevi do not interfere with pupillary dilation or constriction. The diagnosis is often made on clinical grounds. Ancillary tests include iris fluorescein angiography, ultrasound biomicroscopy (UBM), transillumination and anterior segment optical coherence tomography. UBM may measure the thickness of the lesion, show the cystic components and more importantly demonstrate involvement of the ciliary body. Fluorescein angiography is often non-contributory due to heavy pigmentation of nevi but occasionally may reveal diffuse, tortuous and anastomotic vascularization within the tumor. These tests are seldom reliable however in the differential diagnosis and in differentiating benign lesions from the malignant.



Sector iris nevus on a light colored iris.

Pathology

Histopathologically iris nevi are traditionally grouped into 4 subtypes.

Epitheloid cell nevus is composed of intrastromal nests of small, polyhedral cells with basophilic nuclei located near the nuclear membrane.

Intrastromal cell nevus is formed by lightly pigmented ovoid or spindle shaped cells with dot-like nuclei.

Spindle cell nevus has a hypocellular stromal component and a cohesive plaque on the anterior surface of the lesion.

Borderline spindle cell nevus has almost identical features with the former but some cells may have small nuclei. This last subtype may sometimes be interpreted as melanoma. Mitotic activity is absent in all these types of iris nevi.

Treatment

Observation is the preferred management for iris nevi. Approximately 5% of iris nevi show unequivocal evidence of growth in 5 years. Basal diameter larger than 3 mm, documented rapid growth, extraocular extension or invasion of the ciliary body, prominent vascularity, and pigment dispersion and development of high intraocular pressure are all indicators of a suspicious iris melanoma and prompt therapeutic action should be taken.

Prognosis

Systemic and ocular prognoses are excellent in patients with iris nevus.

Disease

Melanocytoma

Note

Alias: Magnocellular nevus

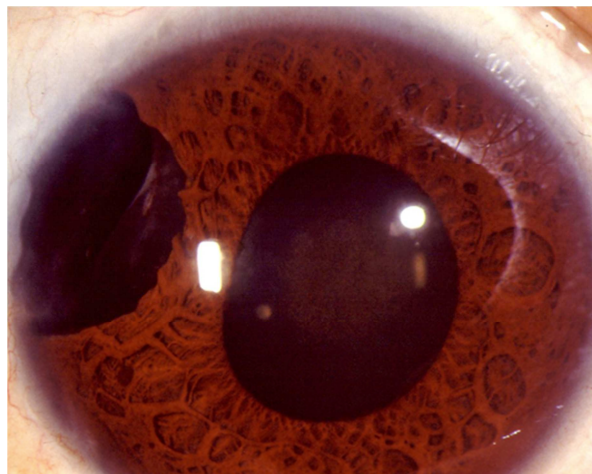
This is a rare type of darkly pigmented melanocytic lesion, generally found on the optic disc, but also described in the choroid, conjunctiva and sclera.

Epidemiology

Usually diagnosed in adults, melanocytomas usually develop in pigmented persons with a female sex predilection.

Clinics

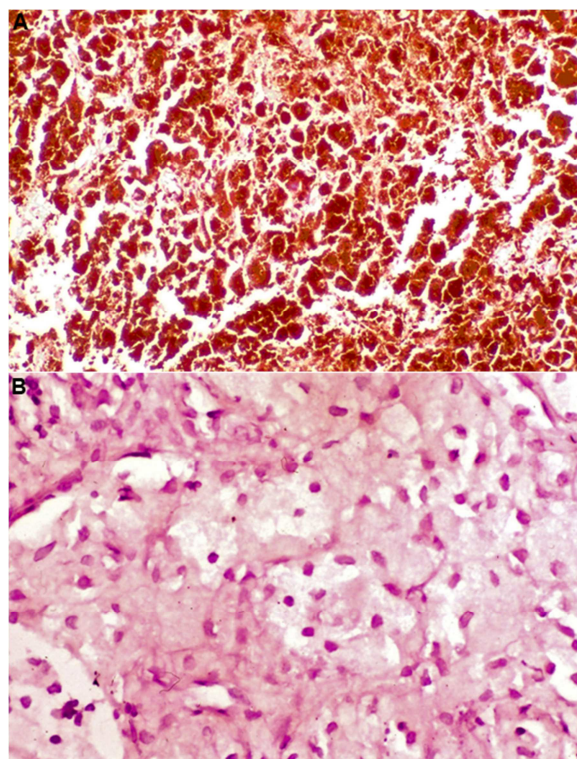
Iris melanocytoma is a solitary deeply pigmented nodular tumor with irregular borders and surface. The majority of the lesions develop in the inferior and lateral parts of the iris and the iris root is particularly involved. In fact, it is believed that 85% of ciliary body melanocytomas erupt into the anterior chamber via the peripheral iris. Melano-cytoma may undergo spontaneous necrosis and macrophages containing large amounts of pigment may obstruct the trabecular meshwork and cause melanocytomalytic glaucoma. This type of glaucoma is often refractory to medical treatment. Other findings include pigment seedings on the iris stroma, iridocorneal angle, anterior chamber and corneal endothelium. The diagnosis of iris melanocytoma is not always straightforward. Most cases are initially classified as iris nevi. Those tumors that grow or extend outside the eye eventually undergo a diagnostic incisional or an excisional biopsy and it is only after the histopathological examination that the diagnosis of melanocytoma is made with certainty. In selected patients, fine needle aspiration biopsy may be helpful in differentiating from melanoma.



Dark brown iris lesion that proved to be a melanocytoma following iridectomy.

Pathology

A melanocytoma is composed of regular, large polyhedral cells with abundant cytoplasm full of pigment. Mitotic figures are usually absent or distinctly few. The nuclear-cytoplasmic ratio is low. Smaller deeply pigmented fusiform cells may also be occasionally encountered. Massive pigmentation almost always impedes the observation of cellular details under light microscopy. This problem is circumvented by appropriate bleaching techniques.



A: Typically, melanocytoma cells are packed with large amounts of melanin pigment which limits the study of further histopathological details. (HE, X 80).

B: After bleaching, the benign character of the plump cells with small, bland nuclei within large cytoplasm can be better appreciated.

Treatment

By virtue of their benign nature, iris melanocytomas are best managed by regular observation. The presence of high intraocular pressure, continuous growth or a strong suspicion for a melanoma mandate surgical excisional biopsy whenever possible. Even after complete removal of the tumor, high intraocular pressure may persist only to subside months later. Enucleation is rarely performed for a melanocytoma.

Prognosis

Melanocytomas have long been considered as benign and stable lesions. However long-term observations now show that there may be a documented growth in 23% of the tumors by 5 years and in 48% of tumors at the end of 10 years. These tumors may even develop extrascleral extensions in which case, differentiating the tumor from a melanoma may become very difficult. On rare occasions, iris melanocytoma may transform into a melanoma. For these reasons close observation is mandatory in patients with iris or iridociliary melanocytomas.

Genes involved and proteins

Note

Lisch nodules are almost always associated with neurofibromatosis type 1 whose gene was cloned on chromosome 17q11.2. There are 3 embedded genes known as EVI2A, EVI2B and oligodendrocyte myelin glycoprotein. The cytoplasmic protein product

is called neurofibromin which controls mammalian target of rapamycin (MTOR). This serine/threonine kinase has a regulatory function on cellular growth and proliferation. Neurofibromin has also a tumor suppressor function by inactivating a cellular proto-oncogene, p21 ras.

References

- Jakobiec FA, Silbert G. Are most iris 'melanomas' really nevi? A clinicopathologic study of 189 lesions. *Arch Ophthalmol*. 1981 Dec;99(12):2117-32
- Ragge NK, Acheson J, Murphree AL. Iris mammillations: significance and associations. *Eye (Lond)*. 1996;10 (Pt 1):86-91
- Fineman MS, Eagle RC Jr, Shields JA, Shields CL, De Potter P. Melanocytolytic glaucoma in eyes with necrotic iris melanocytoma. *Ophthalmology*. 1998 Mar;105(3):492-6
- Eagle RC Jr, Shields JA, Shields CL, Wood MG. Hamartomas of the iris and ciliary epithelium in tuberous sclerosis complex. *Arch Ophthalmol*. 2000 May;118(5):711-5
- Nichols JC, Amato JE, Chung SM. Characteristics of Lisch nodules in patients with neurofibromatosis type 1. *J Pediatr Ophthalmol Strabismus*. 2003 Sep-Oct;40(5):293-6
- Demirci H, Mashayekhi A, Shields CL, Eagle RC Jr, Shields JA. Iris melanocytoma: clinical features and natural course in 47 cases. *Am J Ophthalmol*. 2005 Mar;139(3):468-75

This article should be referenced as such:

Kiratli H. Head and Neck: Iris Hamartomas. *Atlas Genet Cytogenet Oncol Haematol*. 2010; 14(1):83-86.
