Iris Juvenile Xanthogranuloma Studied by Immunohistochemistry and Flow Cytometry

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Abstract. An unusual large tan iris mass in a 19-month-old child was removed by iridocyclectomy and studied by light microscopy, immunohistochemistry, and flow cytometry. The excised mass consisted of granulomatous inflammation with numerous osteoclast-like giant cells and scattered atypical Touton giant cells. Immunohistochemistry studies showed that the cells were most consistent with mononuclear histiocytes. Flow cytometry showed that 90% of the cells sampled were T-lymphocytes, with a predominance of T-suppressor cytotoxic cells. Juvenile xanthogranuloma (JXG) of the iris can occur as a large solitary mass, without signs of intraocular inflammation or hyphema. [Ophthalmic Surg Lasers 1997;28:140–144.]

Juvenile xanthogranuloma (JXG) is a cutaneous eruption of childhood characterized by solitary or multiple, yellow-red, transient papules. It can affect the ocular structures, including the uveal tract, eyelid, conjunctiva, and orbital tissues. The best known ocular involvement is nodular or diffuse infiltration of the iris by a vascular lesion that can bleed, causing a spontaneous hyphema and secondary glaucoma. Iris lesions of JXG have been studied by routine histopathologic methods, but only rarely evaluated with immunohistochemistry or flow cytometry. Further, a systematic approach to the management of iris JXG has not been established. We describe a child with JXG of the iris whose lesion was studied with immunohistochemistry and flow cytometry, and we make recommendations about the management of JXG of the iris.

CASE REPORT

In October 1993, a 19-month-old girl had pink-eye. When it did not respond to treatment with topical antibiotics and corticosteroids, she was referred to one of us (MLZ). The findings of office examination suggested that the left eye was amblyopic. In addition, an unusual mass was seen in the left iris. The patient was referred to the ocular oncology service for further evaluation.

The child had no history or signs of cutaneous lesions. The differential diagnosis included iris JXG, medulloepithelioma, sarcoidosis, melanoma, leukemia, and rhabdomyosarcoma. A complete blood count and a chest x-ray showed normal findings.

On examination under anesthesia, intraocular pressure (IOP) was 18 mm Hg in the right eye and 21 mm Hg in the left eye. A large, solid, tan vascularized iris mass filled the inferior one-half of the anterior chamber of the left eye (Fig. 1). No hyphema was present, and there were no keratic precipitates or other signs of intraocular inflammation.

A diagnostic fine-needle aspiration biopsy (FNAB) was performed. Cytologic study showed lymphocytes and a few eosinophils, but a specific diagnosis was not made. Primary malignancy of the iris could not be excluded. The decision was made to remove the tumor by partial lamellar iridocyclectomy. The tumor was removed, with adequate margins, without complications. A secondary cataract was suc-
Figure 1. Clinical appearance of an anterior segment lesion showing a tan mass filling the inferior one-half of the anterior chamber.

Figure 2. Grossly sectioned specimen showing the yellow hemorrhagic appearance of the mass.

Figure 3. Photomicrograph showing dense infiltration of histiocytes, lymphocytes, plasma cells, and osteoclast-like giant cells (hematoxylin-eosin, ×150).

Figure 4. Photomicrograph showing infiltration of histiocytes, lymphocytes, plasma cells, and Touton-like giant cells (hematoxylin-eosin, ×150).

cessfully removed 8 months later. Although there is continued amblyopia, the vision in the left eye has been partially restored with a contact lens and patching of the right eye. Accurate determination of visual acuity has not been possible because of the patient's age.

Grossly, the specimen was a smooth, tan mass measuring 12 × 7 × 2 mm. On sectioning, it appeared yellow and contained a few focal hemorrhages (Fig. 2). Microscopically, the lesion consisted of a diffuse infiltration of macrophages, epithelioid histiocytes, multinucleated giant cells, lymphocytes, and a few erythrocytes. Most of the giant cells were of the osteoclast type (Fig. 3). Only occasional Touton giant cells with peripheral lipid were present (Fig. 4). There were abundant capillary channels in the mass. There was no evidence of caseation necrosis. Special stains did not show acid-fast organisms, bacteria, or fungi. Immunohistochemical stains performed on tissue fixed in B-5 fixative showed positive immunoreactivity for macrophage markers, lysozyme, alpha-1-antichymotrypsin (ACT; Fig. 5), and MAC 8. Lysozyme and MAC 8 stained small mononuclear histiocytes that were dispersed throughout the infiltrate. Some of the giant cells stained with ACT. The stain for S-100 protein was negative (Fig. 6), excluding other histiocytoses, such as Langerhans' cell histiocytosis and Rosai-Dorfman's sinus histiocytosis.

Because the initial clinical differential diagnosis included leukemia, fresh tissue was submitted for immunophenotypic analysis by flow cytometry. A panel of antibodies selected for the detection of childhood leukemia was used. Flow cytometry showed that 90% of the cells sampled were T-lymphocytes (CD2+). Most of the T-lymphocytes (69%) were CD8+ suppressor cytotoxic cells, which normally account for 20% to 35% of peripheral blood leukocytes. Only 11% were CD4+ helper/suppressor T-cells, which nor-
mally account for 45% of peripheral blood leukocytes. Approximately 8% of the cells sampled were mono-
cytes, based on positivity with the marker CD8.

The final diagnosis was histiocytic infiltration of the iris containing Touton giant cells consistent with
JXG. The histopathologic sections were reviewed by the departments of ophthalmology and der-
matopathology at the Armed Forces Institute of Pathology in Washington, DC, and there was a consen-
sus that the lesion was most consistent with JXG.

**DISCUSSION**

JXG is a dermatologic condition that is character-
ized by multiple cutaneous papules that appear
abruptly and eventually involute. It can also occur in
noncutaneous sites, such as the lungs, pericardium,
viscera, testes, bone, and ocular tissues.\(^1\,^2\,^6\) It can affect
the eyelid, conjunctiva, orbit, and uveal tract.\(^2\,^4\,^6\) The
most common ocular manifestation of JXG is an iris
mass with spontaneous hyphema and secondary glau-
coma.\(^2\,^6\,^8\)

The iris JXG in our patient had some atypical fea-
tures. Clinically, the patient had no history of cuta-
neous lesions, and the iris mass was brown, suggesting
a melanocytic lesion. It was cohesive, did not appear
loose or friable, and had not produced a hyphema,
despite its large size. There were no keratic precipi-
tates, extratymoral iris nodules, or other signs of gran-
ulomatous iritis. From a clinical standpoint, other iris
lesions, such as medulloepithelioma, sarcoid granulo-
ma, melanoma, leukemia, and rhabdomyosarcoma,
could not be excluded. Because the steroid-resistant
mass was large and FNAB did not establish a diagno-
sis, excisional biopsy was considered appropriate
management.

Histopathologically, the infiltrate contained more
lymphocytes and plasma cells than are usually seen
with JXG, and most of the giant cells were not Touton
giant cells. However, based on the presence of a xan-
thogranulomatous lesion with some lipid-containing
giant cells in a young child, the diagnosis of JXG was
preferred by expert ophthalmic and dermatologic
pathologists.

Because of the uncertainty about the clinical diag-
nosis in our case, we performed immunohistochemistry
and flow cytometry. Immunohistochemistry showed
positive immunoreactivity for mononuclear histiocytes
and negative immunoreactivity for S-100 protein, sup-
porting the diagnosis of JXG and excluding Langerhans'
cell histiocytosis. Flow cytometry was performed
because the differential diagnosis included leukemia.
The analysis used antibodies that were appropriate for
evaluation for childhood leukemia. Except for CD8, the
flow cytometry did not use markers for macrophages
and monocytes. For this reason, the study showed a pre-
dominance of lymphocytes, most of which were T-sup-
pressor cells. These results conflict with the immunohis-
tochemical findings of DeBarge and associates,\(^1\) who
found mostly T-helper lymphocytes in addition to
macrophages. The reversal of the normal helper:sup-
pressor cell ratio in our patient initially raised the ques-
tion of human immunodeficiency virus (HIV) infec-
tion. However, the child has remained healthy and has
no known risk factors for HIV. To date, the parents have
declined HIV testing.

The clinical management in this case was difficult.
The FNAB yielded adequate cells for analysis, but
only lymphocytes and plasma cells were identified and
neither lipid histiocytes nor Touton giant cells were
found. In most cases, however, FNAB can establish
the diagnosis. In a previous publication, we reported three cases of JXG that we successfully diagnosed with FNAB, thus avoiding an open biopsy.9

Because JXG of the anterior uvea is uncommon, few clinicians have had experience with more than one case. Consequently, the best management of iris JXG has not been established. Guidelines for treatment would be worthwhile because it can be an aggressive blinding condition in young children. Based on our clinical experience with six cases, our experience with mail consultations and telephone calls from colleagues on other cases, and a review of the literature, we can make some general recommendations about the management of JXG of the iris.

First, every child in whom JXG is suspected should have a thorough skin examination. The parents should be questioned to determine whether there is or has been cutaneous involvement. This involvement would support the ocular diagnosis. Depending on the clinical situation, management options for an anterior uveal lesion include simple observation, topical corticosteroids, oral corticosteroids, FNAB, subconjunctival corticosteroids, and local tumor resection. In cases that do not respond to corticosteroids, irradiation may be necessary.

If a small iris lesion is suspected to be JXG in a child who is asymptomatic and has normal IOP, observation seems to be the best management. Because the natural course of cutaneous JXG is spontaneous regression, it is likely that small iris lesions can show similar regression. This situation has rarely been documented, probably because only larger, more symptomatic lesions are recognized clinically.

If an iris lesion suspected to be JXG is associated with signs of uveitis, but no hyphema or secondary glaucoma, a trial of topical corticosteroids is warranted. Because most types of granulomatous uveitis are sensitive to corticosteroids, it is likely that some cases will show a favorable response.

If there is more severe inflammation, slight hyphema, and secondary glaucoma, the use of oral corticosteroids in appropriate pediatric doses seems justified, especially if the mass does not show a favorable response to topical corticosteroids.

If there is no satisfactory response to oral corticosteroids, then subconjunctival injection of corticosteroids by standard techniques seems justified.12

Examinations under anesthesia may be necessary to administer the drug and to monitor the clinical findings and IOP in the affected eye. Therefore, fine-needle biopsy is an option before subconjunctival corticosteroids are given. Patients treated with corticosteroids should be monitored closely for cataract or glaucoma, even if examination under anesthesia is necessary for accurate tonometry.

Larger lesions that are suspected to be iris JXG and have produced hyphema or secondary glaucoma require a more aggressive approach. In these cases, it is necessary to perform a detailed ocular evaluation to exclude retinoblastoma, leukemia, medulloblastoma, and other causes of iris mass and spontaneous hyphema in a child. Biopsy can be performed on any cutaneous lesion that is suggestive of JXG. If the diagnosis is still uncertain, then FNAB can be performed with a technique reported in the literature.10 However, if retinoblastoma is a strong consideration in the differential diagnosis, FNAB should be avoided if possible.

Localized larger iris lesions that do not respond to corticosteroids or produce uncontrollable secondary glaucoma may be best managed by local resection with iridectomy or iridectomy, depending on the extent of the lesion. There have been no large studies assessing the effectiveness of local resection of iris JXG.

Diffuse unresectable lesions that are unresponsive to corticosteroids can be managed by radiation therapy with the goal of controlling the mass and preventing severe complications of secondary glaucoma. There have been no large studies assessing the role of radiation therapy in such cases. A dose in the range of 300 to 500 cGy has been recommended.13 Although this dose is generally considered safe, there are medical and public concerns about using even small doses of radiation therapy in young children. Brachytherapy with a radioactive plaque may be an option because it is effective in controlling iris malignancy.14

However, ocular irradiation usually should be avoided in children because of the possibility of cataract or glaucoma. It should be considered a last resort in cases of JXG.

If corticosteroids and radiation therapy do not control this disease and the affected eye becomes blind and painful, then enucleation may be justified. Although many cases reported in the literature resulted in enucleation,2,6 we have not yet had to perform enucleation because of failure of more conservative treatment of iris JXG.

If the diagnosis of JXG had been established with FNAB in our case, then oral or subconjunctival corticosteroids could have been used. Because a primary
malignancy could not be excluded, it seemed best to excise the mass completely. Immunohistochemistry and flow cytometry were used to characterize the cells in this case.

REFERENCES