JUVENILE OCULODERMAL XANTHOGRANULOMA*†

BY

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SINCE the initial description of a case of "Nevoxantho-endothelioma with ocular involvement" by Blank, Eglick, and Beerman (1949), the clinical picture of xanthogranuloma as it affects the eye has become well publicized. Almost invariably the disease remains confined to the one eye, but Radian, Radian, and Ostfeld (1964) have reported a bilateral case. A second example in which the disease successively involved the two eyes and which, as a result, posed a difficult therapeutic problem is reported here.

Case History

A baby boy was taken to another hospital at the age of 4 weeks with a history of "yellowness" and watering of the right eye for 2 weeks.

A diagnosis of iritis was made and he was admitted for treatment with oc. atropine 0.5 per cent. and oc. chloramphenicol 8-hrly. There was a slight improvement 4 days later. General examination revealed no abnormality.

The blood count was normal. Blood Wassermann reaction negative. Total serum proteins, 6.8 g. per cent., albumin 5.2 g. per cent., globulin 1.6 g. per cent. Serum electrophoresis showed the γ -globulin reduced to 0.18 g. per cent. (normal range 0.8–1.0 g. per cent. at 4 to 6 weeks, but dropping sharply thereafter).

Local treatment was continued together with a 5-day course of systemic achromycin but without improvement.

On June 9, 1965, he was examined under anaesthesia. The cornea was hazy and enlarged. There was a marked iritis with exudate in the pupil. No view of the fundus was obtained. The intra-ocular pressure was not recorded. Paracentesis was performed in the hope of obtaining a view of the fundus but this was precluded by a total hyphaema. The left eye was normal and remained so throughout this period of hospitalization.

The right eye was enucleated on June 29, 1965.

On November 18, 1965, when he was 8 months old, his mother brought him to the Manchester Royal Eye Hospital saying that his left eye had been red and irritable for 4 days. Apart from the trouble with the right eye his past and family history was uneventful. Examination under anaesthesia the next day revealed moderate injection and an oedematous corneal epithelium. The corneal diameters measured 11 mm. vertically and 12 mm. horizontally. Intra-ocular pressure was 36 mm. Hg (Schiotz). Application of glycerin drops revealed a curious "fluffy" appearance of the whole iris particularly around the pupil and many iris vessels. The fundus could not be seen. He was immediately admitted to hospital for treatment with Syrup Diamox 60 mg. 6-hourly. The diagnosis was uncertain.

The eye was twice re-examined under anaesthesia at weekly intervals. A subconjunctival injection of 25 mg. cortisone was given on the first occasion and on the second two small yellowish

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papules were removed from the back of the neck. If anything, the eye became worse (Fig. 1) and a transient hyphaema was noted.

FIG. 1.—Appearance of left eye, 3 weeks after start of involvement.

Histological Report (JLSS)

During this period sections from the first eye became available and showed the picture of xanthogranuloma; the histology of the small yellowish papules was similar.

Right globe 2.45 cm. in length. Corneal measurements 14 mm. horizontally by 13.5 mm. vertically. Horizontal sections.

FIG. 2.—Histological section of enucleated right eye, showing diffuse cellular infiltration of ciliary body. $\times 45$.

There is some thickening of the ciliary body and its processes—apparently uniform and involving the whole circumference of the ciliary body—due to a diffuse infiltrate of cells of moderate size with lightly staining cytoplasm (Fig. 2). The nuclei are vesicular in type, oval or spindle-shaped, and exhibit moderate numbers of mitoses. The nuclei are erratically disposed, sometimes piled together (Fig. 3) with the formation of occasional giant cells, a few of which are of the Touton type. There is a spattering of small mononuclear cells. Posteriorly the infiltrate thins out gradually, barely reaching to the ora except in the upper temporal sector where it extends almost to the equator. In general there is little thickening of the iris and this is largely confined to the region of the root, notably on the lateral side adjoining the site of paracentesis. In the remainder of the iris, much of the increased cellularity is due to the presence of multinucleate giant cells of non-specific or foreign body type (Fig. 4) and iron-containing pigment derived from old haemorrhage is prominent, notably in the region of the iris root adjoining the filtration meshwork. Patchy

FIG. 3.—Irregular disposition and grouping of cell nuclei in ciliary body. $\times 480$.

FIG. 4.—Multinucleate giant cells and pigment deposits in iris. $\times 480$.

haemorrhage is evident, showing an obvious continuity in places with the hyphaema in the anterior chamber. In the posterior aqueous chamber, pigment-laden phagocytes are numerous in relation to previous haemorrhage. Disturbance of the pigment epithelium is relatively slight and this structure appears intact in the ciliary region.

The angle is closed by the forward expansion of the ciliary body and by adherent peripheral iris which is united to the cornea owing to a number of ruptures in Descemet's membrane. The cornea is oedematous. Extensive posterior synechiae are present though not fully complete on the temporal side, the iris being retracted laterally to give an eccentric pupil. The typical cellular reaction is seen to a limited degree within the anterior scleral canals but the episclera seems uninvolved. As yet any loss of retinal ganglion cells is small.

The chief site of the lesion has been the ciliary body.

Diagnosis.—Xanthogranuloma with secondary buphthalmos.

Treatment.—The choice lay between radiotherapy and a trial of systemic steroids. There was the very remote possibility that the condition in the second eye was an atypical sympathetic ophthal-

mitis, especially in view of the paracentesis of the first eye, and systemic steroids were therefore tried. The following regime was instituted in addition to the Diamox:

Syrup prednisone 15 mg. 6-hrly (*i.e.* 60 mg. per day) together with gutt. atropine 1 per cent. and gutt. Predsol 6-hrly to the eye.

Clinical improvement was seen after 5 days and steady progress was maintained thereafter. A transient nystagmus was noted for a few days but by December 21, 1965, the child was obviously seeing normally and it was considered safe to start reducing the steroids from 60 to 40 mg. per day. A week later the media were clear and the fundus of normal appearance, so that the prednisone was reduced to 30 mg. per day and the Diamox to 60 mg. 8-hrly. The atropine drops were stopped the next day and 3 days later the prednisone was further reduced to 20 mg. and the Diamox to 60 mg. 12-hrly, the latter being stopped altogether on January 1, 1966. The prednisone was reduced 2 days later to 15 mg. per day and after a further 6 days to 10 mg. per day.

On January 14, 1966, he was again examined under anaesthesia and the normality of the eye confirmed. The intra-ocular pressure was 22 mm. Hg (Schiotz). The iris presented a normal blue colour and was without obvious structural disturbances (Fig. 5).

FIG. 5.—Appearance of left eye after local steroid therapy for 4 weeks.

The baby was discharged from hospital on January 18, 1966, on prednisone 5 mg. twice daily; the dose was lowered to 5 mg. once daily after one week and abandoned altogether in another 2 weeks.

Follow-up.—When he was last seen in March, 1967, at the age of 2 years, the eye was quite normal.

Review of Treated Cases

So far as we are aware only twelve reported cases call for consideration.

(1) Newell (1957) described a case in which intra-ocular pressure was not controlled by miotics. Goniotomy and cyclodialysis also failed to reduce the tension but a trephine with peripheral iridectomy was successful. None of these operations produced a hyphaema.

(2) Shusterman (1959) also treated a case successfully by operation, *viz.* goniotomy and goniotomy. The diagnosis was amended from unilateral buphthalmos associated with von Recklinghausen's disease to juvenile xanthogranuloma after biopsy of a skin lesion. There was no hyphaema.

(3) The case reported by Hedges (1959) had no skin lesion and there was no biopsy to confirm the diagnosis. The eye was treated with superficial radiotherapy (400 r) given over a 10-day period. Improvement started 3 days later, and after a month the eye was completely normal.

(4) The first case reported by Maumenee and Longfellow (1960) was maintained on cortisone drops for 5 months during which the iris lesion became bigger. She was then given 600 r to the eye and the local cortisone was continued; 8 weeks later "the iris lesion was still present but appeared less prominent" and 1 year after radiotherapy "the lesion had not changed appreciably". After 3 months, however, the circumcorneal injection had gone and there was no longer any photophobia. The eye was normal $4\frac{1}{2}$ years after the patient was first seen except for a few peripheral lens opacities and a slightly atrophic segment of iris.

(5) Maumenee and Longfellow (1960) reported a second patient who received no ocular treatment until the tension was found to be raised 2 months after he was first seen. Intra-ocular pressure could not be controlled with Diamox and pilocarpine and a goniotomy was performed. Diamox and pilocarpine were continued and 5 days later systemic steroids were started (dosage not given). It is not clear how effective these measures were or how long they were continued, but 11 days later five treatments of 100r were given on consecutive days, and 7 weeks after this the cornea was still hazy and the iris a muddy-brown colour. The ocular tension became normal 15 weeks after radiotherapy; 8 months after the irradiation, the iris was still thickened and vascularized and "the entire central portion of the lens had been absorbed and there was a doughnut-like opacity of cortical and capsular material outside the central 4 mm. pupillary zone". A month later the condition appeared to have largely resolved as the fundus could be easily seen. The authors state that it was not clear whether the cataract was the result of the radiation or of the goniotomy, but they thought the dosage given to *both* their cases was too high.

(6) The case described by Stein (1960) is interesting for several reasons:

- (i) it is the only case reported so far with a sibling who has the skin manifestations (but not the ocular ones);
- (ii) the second eye was affected, although only to the extent of epibulbar plaques;
- (iii) the condition was "active" (typical iris lesions and secondary glaucoma) for at least a year.

This eye was treated with 1 per cent. cortisone drops, but the exact duration of treatment was not stated. Both eyes were normal 7 years later except that the iris of the first eye was slightly darker.

(7) Cleasby (1961) performed an iridectomy in his case, producing a hyphaema. Radiotherapy was given—a total dosage of 600r in three treatments over 7 days. There was considerable improvement within a week, and 3 years later the eye was normal except for some lens changes. He thought the dose of radiation should have been smaller.

(8) Del Buono (1962) treated his case with topical cortisone with little effect. There was some improvement after 15 days of systemic cortisone (dose not given) but the fundus was never visible. We are not told how long this treatment was continued, but, 14 months later, the eye was esotropic and had a partially opaque cornea and the lesion had encompassed the whole iris.

(9) Gass (1964) described a case of a red eye which developed a yellowish lesion and flecks of blood on the iris. Excisional biopsy was performed without producing a hyphaema, and was followed by a month's course of "intensive" doses of Decadron and Gantrisin twice daily. The eye recovered completely.

(10) Moore and Harry (1965) also carried out an excisional biopsy of the iris lesion but this was followed by a full hyphaema and raised intra-ocular pressure. Radiotherapy (two doses of 200r each with a 7-day interval between them) produced considerable improvement 10 days later. There was no recurrence and the eye remained quiet during the following 2 years.

(11) In the bilateral case described by Radian and others (1964), the right eye was badly damaged by glaucoma. Three goniopunctures eventually reduced the ocular tension and radiotherapy (dose not given), reduced the inflammation, but there again the lens was damaged and partly resorbed. This eye became blind. The left eye was successfully treated with radiotherapy (255r in four doses over 18 days). Local treatment had been ineffective in both eyes.

(12) Clements (1966) has recently reported a case successfully treated with Diamox and local steroids alone. Despite lack of histological confirmation this would appear to be an undoubted example and the condition subsided over a period of 3 months.

Other cases have been treated conservatively: *e.g.* Hogan (personal communication to Sanders), (1962) and five of a series of twenty eyes reported by Sanders (1962) were not enucleated, but details of treatment and results are not stated.

Discussion

When considering the treatment of the ocular manifestations of xanthogranuloma one must remember that the severity varies from case to case. At one extreme, eyes have had to be removed relatively early because of intractable glaucoma and at the other extreme a functional eye had resulted after resolution of the disease. In addition to radiotherapy and steroids, surgery has been used and was indeed successful in the cases described by Newell (1957) and Shusterman (1959); surgery may also have contributed, together with systemic steroids, to the successful outcome in the patient reported by Gass (1964). Surgery may precipitate severe haemorrhage into the anterior chamber as in the cases of Cleasby (1961), Moore and Harry (1965), and Maumenee (1956), and in the first eye of the case presented here. In general, however, it would seem unwise to operate on an eye for a condition which numbers spontaneous hyphaema among its clinical characteristics, unless all other treatment has failed.

Radiation is the treatment currently advocated. It was successful in the cases treated by Hedges (1959), Cleasby (1961), Radian and others (1964), and Moore and Harry (1965), though less dramatic effects were produced in the two cases of Maumenee and Longfellow (1960). Indeed, in their first case, the iris lesion had not changed appreciably a year after treatment. The dosage of radiotherapy given to these six cases was 255 to 600r which is somewhat in excess of what is claimed to be the maximum safe dosage—*i.e.* 175r (Merriam and Focht, 1957). Radiation was also successful in the treatment of an epibulbar lesion (report of case AFIP.ACC 972404—Zimmerman, 1965).

Amongst others, the case of Gharib, Burke, and Brunsting (1959) shows that the lesion will resolve spontaneously in the course of time as always occurs with the skin lesions. The cases of Stein (1960) and of Clements (1966) seem to have run a benign course and cortisone drops were sufficient to tide these eyes over until spontaneous resolution occurred. Local steroids were ineffective in both the cases of Maumenee and Longfellow (1960), as were systemic steroids in the second (though there was a long delay before

treatment was instituted). Del Buono (1962) had no success with topical and systemic cortisone but again the dosage is not stated.

The principles of treatment must be to limit or stop the inflammatory reaction in the anterior aspect of the eye and, when necessary, to reduce the intra-ocular pressure, preferably by medical means. The radiation so far used is classed by radiotherapists as a "mild anti-inflammatory" dose, and the clinical evidence so far available suggests that systemic and local steroids, when given in sufficiently high doses, are the more reliable form of therapy and this should become apparent as new cases are reported.

From the histological view point, there is now general agreement that the basic lesion is a proliferation of histiocytic cells, giving often a very uniform picture and thereby tending to stimulate a neoplasm. Thus, Zimmerman (1965) stated "the iris and variable portions of the contiguous ciliary body are infiltrated by histiocytic cells of moderate size, which for the most part have polygonal outlines. Spindle-shaped cells are less commonly observed than in the cutaneous lesions. The histiocytic cells exhibit relatively little pleomorphism and they possess rather small uniform nuclei".

Where proliferative activity is marked, mitotic figures may be relatively numerous—enhancing the "neoplastic look". Congested and dilated vessels are prominent, though the amount of new vessel formation would seem to have been exaggerated, and this is localized mainly to the clinically visible anterior iris surface. This and the almost total absence of any fibroblastic response makes for the preservation of the basic architecture of the anterior uvea, notably of the musculature. Despite the heavy infiltration of the ciliary body in this case, the pattern of the ciliary muscle is easily seen (Fig. 6). On the basis of these simple facts the disorder seems particularly well suited to suppressive steroid medication, especially as there is no question of infection and as the disease is known to be self limiting. One might reasonably expect virtually complete resolution as seems to have happened here.

FIG. 6.—Separation of fibre bundles by proliferating cells in ciliary muscle. $\times 480$.

The case of Shusterman (1959) is notable for the ample foamy cytoplasm of the infiltrating cells, and this degree of lipid storage would suggest a particularly low grade lesion and one controllable, at least in large measure, by local treatment alone.

Summary

A case of bilateral ocular xanthogranuloma with two small skin lesions in a baby boy is reported. One eye was enucleated. The treatment and pathology of the condition is reviewed, particularly in relation to the use of corticosteroids. The dramatic response of the second eye to high dosage with prednisone suggests that this may be the ideal therapy and, as the dosage can be reduced rapidly, untoward long-term sequelae may be obviated. Certainly, in our case, there are no apparent side-effects from the dosage used and the treatment was highly effective.

The patient was admitted to the Manchester Royal Eye Hospital under the care of Mr. A. Stewart Scott, and we wish to thank him for his permission and encouragement to publish the case.

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