Ligneous conjunctivitis

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Ligneous conjunctivitis is a rare form of conjunctival disease which derives its name from the fact that the eyelids are classically described as feeling woody on palpation. The essential feature of the condition, however, is the presence of an irregular elevated mass of hyalinized connective tissue which arises from the affected conjunctiva.

One of the earliest references to what would seem to have been this condition was by von Graefe (1854) and altogether about fifty cases have now been described in the literature. Borel (1933) gave the condition its distinctive name, but since then several other descriptive terms have been used. Verhoeff (1958) coined the term "recurrent post-membranous granuloma of the palpebral conjunctiva" which, although long, summarizes the clinical features of a pseudo-membranous or membranous conjunctivitis followed by the development of an indurated plaque which usually recurs rapidly despite repeated abscissions.

Ligneous conjunctivitis tends to occur in young children, mainly females, and may affect other members of the same family. It is often bilateral and corneal involvement leading to loss of the eye may be a complication. The aetiology is unknown. Howe (1897) gave a pathological description of a conjunctival membrane and suggested a bacteriological approach to diagnosis. Many agents have been suggested as being responsible for the lesion, but although an infective process would seem likely, as in many other varieties of conjunctivitis, no satisfactory proof of this has so far been produced. Several different types of bacteria have, in fact, been isolated from affected eyes, but sterilization of the conjunctiva has neither cured nor prevented further membrane formation and the organisms have been considered to be incidental to the disease. The association in some of the reported cases of systemic signs, such as nasopharyngitis and vaginitis, has suggested a virus aetiology, but this again is unconfirmed. Attempts to isolate rickettsiae and fungi have also been unsuccessful. In the treatment of the condition many varieties of both medical and surgical methods have been used, ranging from the simple instillation of antibiotic drops to excision of all the involved parts followed by a grafting procedure. The results of therapy, however, tend to be disappointing.

Case reports

Case 1, a 5-week-old baby boy, was seen at the Royal Eye Hospital, London in July, 1965. His left eye had been swollen and discharging for about 3 weeks, the condition having developed during the postnatal period in the maternity unit.

Examination

The right eye was normal with no discharge. The left eye showed a moderate degree of swelling of the upper and lower lids and a heavy mucopurulent exudate appeared to be adherent to the tarsal

conjunctiva. The cornea and intraocular tissues were not involved and there was no regional lymphadenopathy. The general condition of the child was satisfactory.

Progress

After admission to hospital and vigorous treatment with irrigations, topical antibiotics, and systemic sulphonamides, the discharge rapidly lessened and by the next day it was noted that a large cheesy mass of what appeared to be granulation tissue was protruding downwards from the upper lid to cover most of the cornea. A similar but smaller mass was seen to be arising from the tarsal conjunctiva of the lower lid. These were considered to be either true or pseudo-membranes. The lower lesion gradually became smaller and disappeared, but the upper one persisted unaltered. There was also a mild sticky discharge from the eye.

After a month, the mass from the upper lid was removed under general anaesthesia. The condition, however, returned to its former state within 3 days, and 2 months later a second excision was performed and the base of the denuded area was painted with silver nitrate. At these two operations the excision involved removal of the tissue from the whole inner surface of the upper lid and fornix. There was a little bleeding from the cut surface and the removed specimens were soft and fleshy.

Following the second operative procedure, a mass returned within 3 days, but clinically this appeared dry and encrusted. During the following months this mass gradually became smaller and it had disappeared completely by the time the child was 9 months old. Throughout the whole of this period local treatment with various antibiotic preparations and simple lotions was maintained. This made no obvious difference to the appearance of the membrane, but the discharge from the eye was less noticeable. The child was last seen when 21 months old and both eyes and adnexae were then quite normal.

Histological examination

The material removed from the lid on the second occasion was submitted for histological examination (Figs 1-3). Sections showed a mass consisting of irregular, non-birefringent, eosinophilic, hyalinized deposits associated with granulation tissue. Both acute and chronic inflammatory cells were seen and in some areas eosinophils were conspicuous. There was, in addition, a little haemorrhage. Islands and strands of partly degenerate epithelium were incorporated within the mass which was also partly covered at the periphery by epithelium. The eosinophilic areas stained bright red with Picro-Mallory stain, thus demonstrating the fibrinous nature of the deposit, but otherwise differential staining revealed neither amyloid nor mucin. No bacteria or fungi were demonstrable.

CONJUNCTIVAL CULTURES Pneumococci and coagulase-positive *Staphylococcus aureus* were cultured on several occasions, but these were sparse growths and unrelated to any obvious change in the condition of the membrane. No fungi were isolated on either blood-agar or Sabouraud's medium.

CONJUNCTIVAL SMEARS No inclusion bodies of the TRIC type were found.

BLOOD EXAMINATION Haemoglobin: 11.8 g./100 ml. = 80 per cent. Total white cell count 7,100/cu. mm.—differential normal. Erythrocyte sedimentation rate: 7 mm. in 1 hour.

Case 2, a young woman aged 18 years, first attended Sutton General Hospital, Surrey, in February, 1967, complaining of a swelling under the right upper eyelid. This had been present for a few weeks, but had caused little discomfort apart from a slight sensation of heaviness in the lid. There were no other symptoms. It was stated by the patient's mother that a membrane had been present beneath the right upper lid when she was 2 weeks old. This had recurred after being removed in hospital on three occasions and did not disappear completely until the patient was 10 months old. Between this time and the present attendance, there had been no further ocular complaints.

FIG. 1 *Islands of epithelial cells incorporated within a mass of inflamed granulation tissue and eosinophilic, hyalinized deposit. Haematoxylin and eosin $\times 85$*

FIG. 2 *Eosinophilic, hyalinized deposit. Haematoxylin and eosin $\times 420$*

FIG. 3 *Inflamed granulation tissue. Haematoxylin and eosin $\times 420$*

Examination

Visual acuity in each eye was 6/6 unaided. The left eye was normal in all respects. Eversion of the right upper lid revealed an elevated hard mass with an indurated base arising from the tarsal conjunctiva (Fig. 4). There was no ptosis, the lower lid was normal, and no other ocular abnormality was detected. There was no regional lymphadenopathy and general physical examination revealed no abnormality.

FIG. 4 *Elevated hard mass arising from tarsal conjunctiva of right upper lid*

Progress

A week after the patient's first visit to hospital, the mass was excised flush with the adjacent conjunctival surface and the bed was noted to be granular and bleeding. Within a week, however, the mass had regrown to its original size. The patient continued to be observed and 3 months later a further excision of the mass was performed. After this procedure there was no rapid recurrence, but a mucoid exudate was seen to be forming at the operation site. In an attempt to clear this exudate, 20 per cent. acetylcysteine drops (a mucolytic agent) were instilled into the affected eye six times a day. The treatment was begun on the ninth postoperative day, but in spite of this the mass gradually reformed and grew to its original size within 3 weeks. There has since been no obvious change and the patient is continuing to be observed.

Histological examination

Sections of the first mass to be excised showed granulation tissue together with an eosinophilic, hyalinized deposit. No epithelium was seen and no micro-organisms were demonstrable.

The second mass to be excised was submitted to a more extensive histopathological study (Figs 5-7, opposite).

Sections again showed granulation tissue in which large numbers of blood vessels were present. Both acute and chronic inflammatory cells were seen, there was some haemorrhage, and inflamed degenerate epithelium was present. Irregular deposits of non-birefringent eosinophilic, hyalinized material as seen in Case 1 were a conspicuous feature and Picro-Mallory stain again showed these to be of a fibrinous nature. As in Case 1, other differential stains for amyloid and mucin were negative and bacteria and fungi were not demonstrable.

Electron microscopy

Electron-microscopical studies were carried out on a small portion of the material removed on the second occasion. It was seen that beaded filaments were laterally aligned to form banded

(5)

(6)

FIG. 5 Large irregular areas of eosinophilic, hyalinized tissue with associated inflammation. Haematoxylin and eosin $\times 85$

FIG. 6 Acute and chronic inflammatory cell infiltrate. Haematoxylin and eosin $\times 420$

(7)

FIG. 7 Inflamed degenerate epithelium. Haematoxylin and eosin $\times 420$

fibrils having a periodicity of 200 Å. The fibrinous nature of the deposit was thus confirmed (Fig. 8, overleaf). There was no evidence to suggest the presence of a virus.

CONJUNCTIVAL CULTURES No bacteria or fungi were grown on blood-agar.

CONJUNCTIVAL SMEARS No TRIC inclusion bodies were seen.

BLOOD EXAMINATION Haemoglobin: 12.5 g./100 ml. = 84 per cent. Total white cell count: 5,800/cu. mm. Erythrocyte sedimentation rate: 8 mm. in 1 hour. Total protein: 7.6 g./100 ml. Electrophoretic strip of serum proteins showed a slight increase in α_2 globulins. Alkaline phosphatase: 6 units/100 ml. Zinc turbidity: 2 units/100 ml. Direct bilirubin: negative. Total bilirubin: 0.5 mg./100 ml. Lupus erythematosus cells not present.

Immunological studies

IMMUNOFLUORESCENCE TESTS Sections 5 μ thick were cut from the excised mass, fixed in cold alcohol, and treated by the direct and indirect immunofluorescent technique using antihuman immunoglobulin fluorescein conjugate. Fluorescence of hyaline bodies was observed, but this

FIG. 8 *Electron micrograph illustrating fine fibrillar nature of deposit. Fibrils show banding at periodicity of 200 Å. Zetterqvist buffered osmium tetroxide fixed-araldite/epon embedded. $\times 45,000$*

proved to be an autofluorescence since the intensity of fluorescence was the same as that seen on examination of an untreated section. Blocking tests failed to eliminate or decrease the intensity of fluorescence. Thus immunoglobulin binding could not be demonstrated in the specimen.

IMMUNOGLOBULIN SERUM ESTIMATIONS These were as follows, the corresponding normal figures as estimated by the same laboratory being in brackets:

Immunoglobulin G	= 650 mg. per cent.	(1,286)
Immunoglobulin A	= 190 mg. per cent.	(175)
Immunoglobulin M	= 170 mg. per cent.	(74)

These figures are not suggestive of an autoimmune mechanism.

Virus studies

TISSUE CULTURES A throat swab and also a part of the excised tissue from the lid were examined for the presence of virus by the inoculation of primary monkey kidney, primary human amnion, and HeLa cell tissue cultures, and by the inoculation of the yolk sac of 7-day-old fertile hens' eggs. All the results were negative.

SERUM ANTIBODIES

Complement-fixation tests			
Antigen	Titre	Antigen	Titre
Influenza A	} < 1/10	<i>C. burnettii</i>	} < 1/10
Influenza B		Respiratory syncytial virus	
Influenza C		Measles	
Sendoi		Eaton's agent	
Parainfluenza 3		Adenovirus	
Psittacosis-LVG		Mumps "S"	
		Mumps "V"	

There was thus no evidence of infection with any of these viruses.

Discussion

Conjunctivitis with membrane formation can result from many different causes. Hogan (1947) classified chronic ligneous conjunctivitis as a membranous conjunctivitis due to unknown or uncertain causes, but suggested that some of the reported cases were due to micro-organisms. He believed that most of them were of streptococcal origin, and considered that future cases would be classified among the other recognized groups of bacterial conjunctivitis. Verhoeff (1958), in describing a chronic case of ligneous conjunctivitis and reviewing the literature relating to the condition, stated that there was usually an associated nasopharyngitis, and considered that the primary infectious agent was probably a filterable virus.

Apart from the apparent absence of upper respiratory involvement, the two cases described in this paper are fairly typical, from both the clinical and pathological viewpoints, of ligneous conjunctivitis. Thus Case 1 was a persistent membranous conjunctivitis appearing in an infant, and Case 2 had a childhood history of what was probably a membranous conjunctivitis, but presented again in adult life with a hard and elevated lid lesion. Neither of the patients, however, had corneal lesions, the presence of which are mentioned by Paufigue and Moreau (1953) as a cardinal sign of the disease. The absence of systemic features and the involvement of only one eyelid may account for this, for in the more severe variety of the condition with a tendency to perforation of the globe, involvement of all four eyelids and extra-ocular manifestations are more common. In this respect it is of interest to note that the case described by Verhoeff (1958) had conjunctival lesions for over 30 years without impairment of vision, and no mention is made of any systemic symptoms. It seems likely that, as suggested by François (1966), there are two varieties of the condition, one with and one without associated systemic disturbances.

Despite the fairly extensive investigations undertaken, particularly in Case 2, no further light has been shed on the question of the aetiology of the condition. The bacteria cultured from the conjunctival sac in Case 1 are considered to be incidental to the disease, and there is thus no convincing evidence of a causative agent in either case.

The possibility that an autoimmune mechanism might be involved in the disease was considered. Neither case, however, showed a raised ESR, and in Case 2 attempts to

demonstrate circulating immunoglobulins and cell-bound antibodies failed to reveal evidence of autoimmunity.

Many of the cases of ligneous conjunctivitis previously described (Goldmann and Hoffer, 1954; Paufigue and Moreau, 1953; Winter and Michler, 1953) show a familial and hereditary tendency. In addition, Winter and Michler (1953) were able to produce a membrane by trauma in their cases and this evidence tended to suggest that membrane formation might have been due not only to hereditary susceptibility but to some abnormal tissue response to injury. Factors likely to have resulted in this response, however, were not suggested. François (1966) demonstrated mucopolysaccharide material in tissue from a biopsy of ligneous conjunctivitis, and in view of this he felt that a disturbance in the metabolism of the conjunctiva, perhaps with a hereditary basis, was the main factor in the aetiology of the condition.

The histopathological findings in the cases under discussion appear to differ little from those previously described. There is a fibrinous deposit associated with a degree of inflammatory cell infiltration and the later development of a hyalinized mass of connective tissue, these changes being secondary to increased permeability of the conjunctival blood vessels with an outpouring of serofibrinous transudate which subsequently undergoes coagulation with the resultant formation of granulation and connective tissue. The factors responsible for this increased vascular permeability, however, are at present unknown, but an autoimmune mechanism should not be excluded on the basis of negative findings in Case 2, and further investigations along these lines are indicated in future cases.

As regards treatment of the condition, the position is still very unsatisfactory. Apart from surgical removal of the membranous mass, other treatments which have given some measure of success include irrigations with streptodornase, streptokinase, and hyaluronidase. Spaeth (1967) recently reported a case which showed limited improvement after combined treatment with idoxuridine and cytosine arabinoside and the simultaneous administration of systemic and topical corticosteroids. The application of β rays and x rays after excision of the mass has been tried but with only a limited degree of success. Héry, Demailly, and Dhermy (1966) recommend an extensive procedure of complete removal of the lesion from the affected lid to leave only skin, and the application of buccal graft to the bare area, followed by x -irradiation. It is felt, however, that such an operation is not indicated if the patient remains relatively free from symptoms.

In Case 1 the mass resolved spontaneously after a period of about 9 months although the regular use of antibiotics may have expedited its cure and prevented keratitis. It is interesting to speculate whether a recurrence will be seen at a later date. In Case 2 the situation remains unaltered. A postoperative course of mucolytic eye drops was given in an attempt to prevent recurrence after the second abscission, but without success. In view of the lack of symptoms it is not proposed to perform any further surgery at present.

In conclusion, the question of nomenclature of this condition should be considered. As pointed out by Verhoeff (1958), the term "chronic membranous conjunctivitis" is inaccurate, for in the stage when the disease is inflammatory and membranous it is not chronic but acute, and when it becomes chronic it is not inflammatory. In the absence of any specific histopathological change and with the aetiology uncertain, in order to distinguish this disorder from chronic conjunctivitis with membrane formation in which the aetiology is known, the only alternative name we would suggest is "idiopathic recurrent membranous conjunctivitis". In the present state of our knowledge, however, there seems little advantage in changing the accepted but rather unsuitable term of ligneous conjunctivitis.

Summary

The general features of ligneous conjunctivitis are mentioned. Two cases of the condition are described. Investigations as to aetiology are considered, and particular reference is made to the possibility of a virus infection or an autoimmune process. Other possible causative factors are mentioned. The unsatisfactory state of present methods of treatment are noted, and it is considered that in the absence of severe symptoms radical surgical treatment is not indicated. The question of terminology is discussed.

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