Poster No: 9

Mucous Membrane Pemphigoid with Ocular Involvement: The Clinical Phenotype and Its Relationship to Direct Immunofluorescence Findings

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BACKGROUND

- **Mucous membrane pemphigoid (MMP)** is a heterogeneous group of autoimmune subepidermal blistering disorders that can affect any mucous membrane, such as the ocular mucosa, oral cavity, and mucous membranes of the respiratory, digestive and genitourinary systems.[1]
- Sites affected are characterized by chronic inflammation with recurrent flare-ups and progressive cicatrization (scarring).
- The reported incidence of MMP is approximately 1.16 to 2.0 per million population.[2,3]
- The mean age of onset of MMP is 65 years.[4,5] However, in children and young adults the disease appears to be more aggressive.[6-8]

Significance of ocular disease

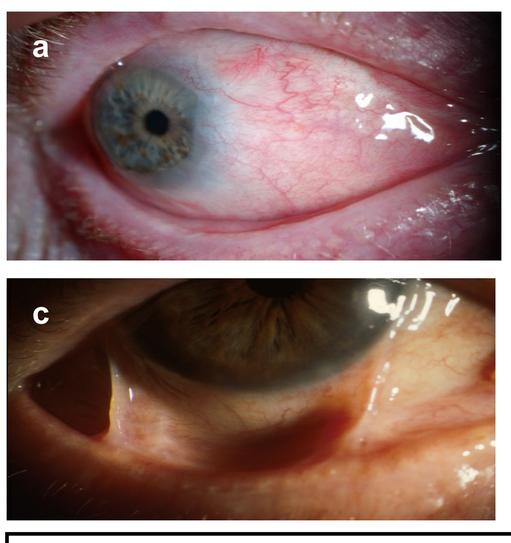
- Ocular involvement, also known as **ocular MMP**, is seen in approximately 70% of MMP cases.[9,10]
- Ocular MMP is the commonest cause of cicatricial conjunctivitis in the UK with an incidence of 0.8 per million population.[11]
- The condition often affects both eyes to varying severities.
- It is characterized by progressive relapsing conjunctivitis with conjunctival cicatrization.
- In severe disease, ocular surface failure, corneal vascularization, and corneal scarring can result.
- Blindness is reported to occur in at least 20% of cases.[12,13]
- To prevent sight-threatening complications in ocular MMP, early diagnosis and commencement of treatment are essential.
- Misdiagnosis, or delayed diagnosis, of ocular MMP leads to the **inappropriate use of topical therapy**, the standard of care for other causes of cicatrising conjunctivitis, rather than **systemic immunomodulatory therapy**; resulting in irreversible clinical deterioration in MMP patients.

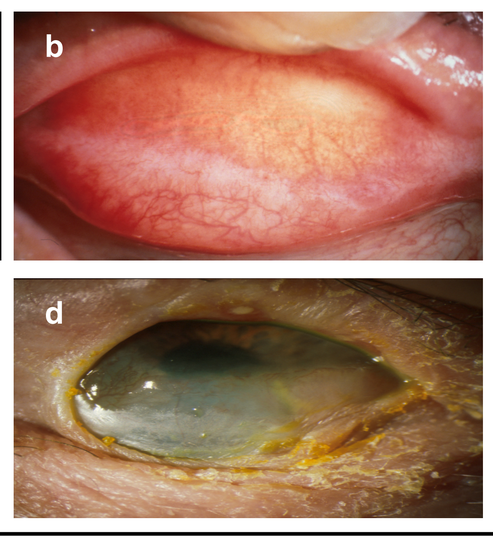
Diagnosis of MMP: a dilemma for the management of patients with negative immunopathology

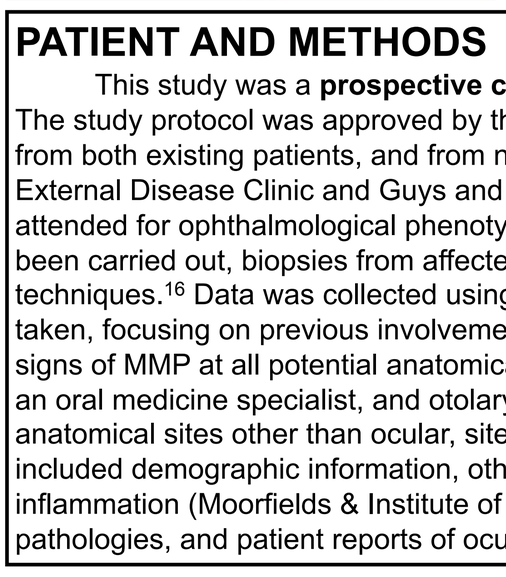
- Strong recommendation from an influential consensus document that laboratory evidence of an autoimmune disease process, with a biopsy from at least one site (skin, buccal, genital, nasopharyngeal, or conjunctival mucosa) being positive on **direct immunofluorescence (DIF),** has is a mandatory requirement for the diagnosis of MMP.[1]
- DIF is almost always positive in MMP that involves tissues other than the eye.
- However, conjunctival DIF is positive in only 25/49 (51%) cases of **ocular only MMP** (in whom the conjunctiva is the only site of involvement).[5,14,15] 13/49 (26%) require **multiple biopsies** to obtain a positive result.[5,14,15]
- Thus, ocular only MMP cannot be excluded by a negative DIF result.
- Alternatively, **indirect immunofluorescence (IIF)** to identify circulating autoantibodies in patients' serum can be diagnostic if positive,[1] although the sensitivities of current IIF techniques are poor.
- Even when conjunctiva, the best available substrate for patients with ocular only disease, is used, only 3/49 (6%) of samples yield positive results.[5,14,15]

Negative immunopathology results have long been recognised as a diagnostic problem in patients with strong clinical evidence of **ocular only MMP**. [Fig. 1] In current practice, there are differences in opinions amongst clinicians of what constitutes a diagnosis of ocular MMP in patients with typical cicatricial conjunctival diseases but consistently negative immunopathological tests. There are currently two view points on these patients: 1) these patients have a disease entity different to those who have positive immunopathological status; or 2) immunopathology techniques are too insensitive to detect the low level of antibodies in these patients. There are currently no studies investigating the **phenotypes** of patients with ocular MMP to suggest that patients who are negative on immunofluorescence have a disease entity different to those who have positive immunopathological results. It is also unclear if the status of patients' immunopathological tests is associated with the severity of ocular disease.

AIM To establish whether there is evidence that patients who are negative on immunofluorescence testing are different from those who have positive immunopathologies, in both **clinical phenotype** and **disease severity**.







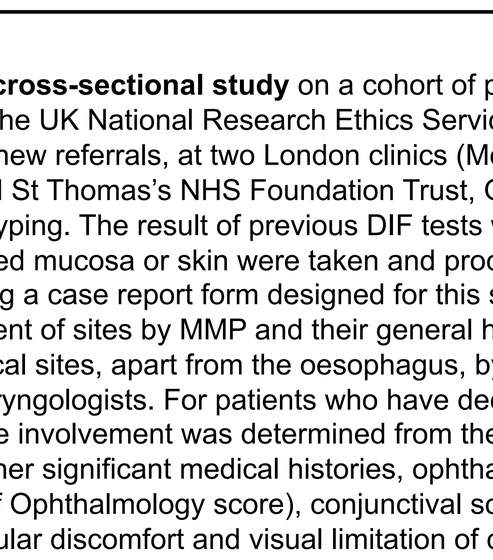


Figure 1 Characteristic features of ocular MMP

a) Chronic conjunctivitis with loss of plica semilunaris (result of subtle scarring)

b) Subtarsal subepithelial conjunctival fibrosis

c) Symblephara

d) Ankyloblepharon with corneal keratinisation

PATIENT AND METHODS

This study was a **prospective cross-sectional study** on a cohort of patients diagnosed with ocular MMP. The study protocol was approved by the UK National Research Ethics Service. MMP patients were recruited from both existing patients, and from new referrals, at two London clinics (Moorfields Eye Hospital, Corneal and External Disease Clinic and Guys and St Thomas's NHS Foundation Trust, Oral Medicine Clinic). Patients attended for ophthalmological phenotyping. The result of previous DIF tests was recorded and, if this had not been carried out, biopsies from affected mucosa or skin were taken and processed for DIF using standard techniques.[16] Data was collected using a case report form designed for this study. All MMP patients had a history taken, focusing on previous involvement of sites by MMP and their general health, and had an examination for signs of MMP at all potential anatomical sites, apart from the oesophagus, by ophthalmologists, a dermatologist, an oral medicine specialist, and otolaryngologists. For patients who have declined screening of particular anatomical sites other than ocular, site involvement was determined from the disease history. Data collected included demographic information, other significant medical histories, ophthalmic history, ocular surface inflammation (Moorfields & Institute of Ophthalmology score), conjunctival scarring (Tauber staging), corneal pathologies, and patient reports of ocular discomfort and visual limitation of daily activities.

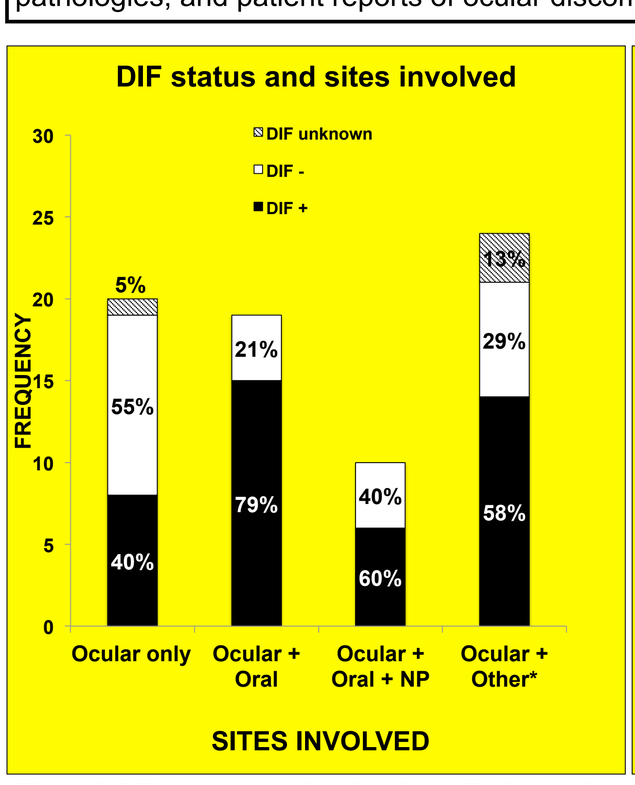


Figure 2 DIF status and sites involved; Patients who had ocular only MMP were more likely to have a negative DIF status (Chi-square, p=0.033); *Oral, nasopharyngeal, skin, anogenital involvement in various combinations

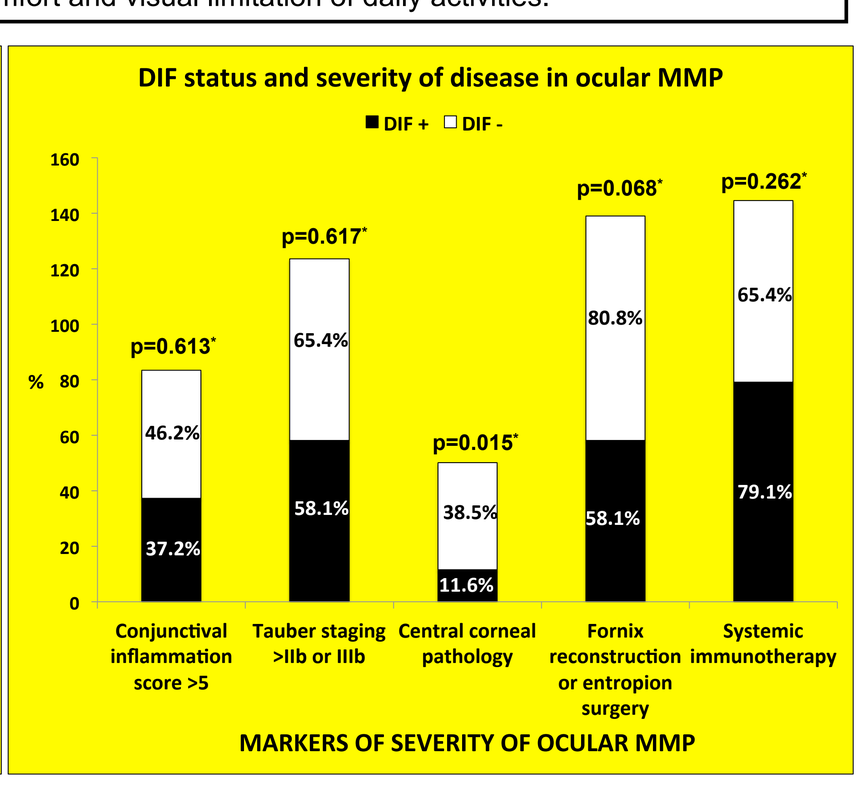


Figure 3 DIF status and severity of disease showing trends of worse severity in DIF negative patients; *Chi-square test

RESULTS

This study included a cohort of 112 patients with a diagnosis of MMP. 73/112 (65.2%) patients screened had MMP with ocular involvement (ocular MMP). The median time from diagnosis to being examined in this cross-sectional study was 104 months (interquartile range [IQR] 54 – 146 months).

Patient characteristics [Table1]

27/73 (37.0%) were female patients. The median age at the time of screening was 60.0 years (IQR 52.5 – 69.0 years). 63/73 (86.3%) were of Caucasian origin. 27/73 (37.0%) had a history of autoimmune disease and 9/73 (12.3%) had a history of malignancy.

DIF status

DIF results were available in 69/73 (94.5%) patients with ocular MMP. Direct immunofluorescence was positive for at least one site in 43/69 (62.3%) of cases. 26/69 (37.7%) patients had negative DIF. In 4 patients, DIF results were uncertain. There were no significant differences in characteristics between the DIF positive and DIF negative patients. [Table 1]

Sites involved

20/73 (27.4%) had **ocular only disease**, 19/73 (26.0%) **ocular and oral disease**, 10/73 (13.7%) **ocular, oral and nasopharyngeal disease**, and 24/73 (32.9%) **ocular and other sites** involvement (oral, nasopharyngeal, skin, anogenital in various combinations). The DIF status of all patients and for the different sites of involvement is illustrated in Figure 2. Patients who had ocular only involvement were more likely to have a negative DIF status (p=0.03).

Severity of disease [Fig. 3]

Reported **ocular discomfort scores** were similar in both DIF positive and DIF negative patients (p=0.10). 12/26 (46.2%) of DIF negative patients had **conjunctival inflammation scores** greater than 5 compared to 16/43 (37.2%) of DIF positive patients (p=0.61). For **conjunctival scarring**, 17/26 (65.4%) of DIF negative patients had Tauber staging of worse than IIb or IIIb in the worse eye compared to 25/43 (58.1%) of DIF positive patients (p=0.62). 21/26 (80.8%) of DIF negative patients required **fornix reconstruction surgery** compared to 25/43 (58.1%) of DIF positive patients (p=0.07). 10/26 (38.5%) of DIF negative patients had **central corneal pathologies** compared to 5/43 (11.6%) of DIF positive patients (p=0.02).

Visual outcomes

Comparing the phenotypes of all patients who had positive DIF with those who had negative status, **visual acuity scores** were statistically worse in patients who were DIF negative (p=0.03). This was not significant when patients with similar sites of involvement were compared. There were no significant differences in the proportion of patients who reported **restriction of daily activities** due to poor vision (p=0.26).

Table 1 Patient characteristics and DIF status

Baseline characteristics	DIF+ positive (n=43)	DIF+ negative (n=26)	DIF+ unknown (n=4)	Significance ‡
Age in years (range, median, interquartile range)	18 - 86, 58.0, 52 – 64	23 - 82, 60.5, 51 – 71	53 - 70, 66.5, 60 – 69	p = 0.620§
Females (n, %)	14, 32.6	12, 46.2	1, 25.0	p = 0.259‖
Race (n, %)				
White-British	33, 76.7	21, 80.8	4, 100	
White-Irish	2, 4.7	0	0	
White-Other	2, 4.7	1, 3.9	0	
Black-African	0	1, 3.9	0	p = 0.566**
Asian-Indian	1, 2.3	1, 3.9	0	
Asian-Pakistani	1, 2.3	0	0	
Other	1, 2.3	2, 7.7	0	
Unknown	3, 7.0	0	0	
Autoimmune disease (n, %)				
Yes	16, 37.2	8, 30.8	3, 75.0	p = 0.586‖
No	27, 62.8	18, 69.2	1, 25.0	
Cancer (n, %)				
Yes	6, 14.0	3, 11.5	0	p > 0.999**
No	37, 86.1	23, 88.5	4, 100	
Ocular co-morbidities				
Glaucoma	8, 18.6	4, 15.4	1, 25.0	p > 0.999**
Pseudophakia	13, 30.2	14, 5.4	0	p = 0.075**
Previous lid surgery	21, 48.8	13, 50	1, 25.0	p > 0.999**
Previous conjunctival surgery	6, 14.0	6, 23.1	0	p = 0.347**
Previous glaucoma surgery	1, 2.3	0	1, 25.0	p > 0.999**
Corneal graft	0	3, 11.5	0	p = 0.050**
Other eye surgery	4, 9.3	4, 15.4	0	p = 0.464**
Other eye disease	1, 2.3	1, 3.9	0	p > 0.999**

*Direct immunofluorescence results ‡Comparing DIF postive and DIF negative patients §Mann-Whitney U test ‖Chi-square test **Fisher's exact test

CONCLUSIONS

- Ocular MMP patients with negative DIF have phenotypes as severe as, or worse, than patients with positive DIF.
- Findings do not support classification of DIF negative patients meeting the clinical criteria for ocular MMP, as having a different disease.
- This category of patients should be accepted as having **DIF negative MMP** for clinical management purposes and avoid delay in treatment.
- Current immunopathology techniques may be too **insensitive** to be used to exclude a diagnosis of MMP when results are negative.
- **Cell mediated response** resulting from autoreactive T cells to epithelial basement membrane proteins, without circulating antibodies.

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