MULTIPLE AUTOIMMUNE DISEASES

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ABSTRACT

Purpose and Methods: Multiple autoimmune disorders occur with increased frequency in patients with a previous history of another autoimmune disease. We present the patient who initially presented with ocular cicatricial pemphigoid OU, history of hypothyroidism and chronic erosive ulcers in the mouth. Continued follow up, careful examination and repeated biopsies of the mouth ulcers reveal lichen planus of the mouth. Conclusion: This case highlights the need for awareness of the possibility of multiple autoimmune phenomena which also indicates the need for continued surveillance for the development of new autoimmune diseases in predisposed patients.

CLINICAL CASE

This is a case of 71 year old white female who was referred by her primary ophthalmologist for evaluation and management of probable ocular cicatricial pemphigoid (OCP) in both eyes. She had had intermittent episodes of blepharitis and conjunctivitis OU for 6 years which were relieved with Tobrex. Recurrent sores of lips, tongue and under the nose were noted. She also complained of mild discomfort on swallowing. An esophagoscopy and esophageal biopsy had been performed in 1993. The results were non diagnostic.

Her past medical history was significant for epilepsy since early childhood and hypothyroidism diagnosed a few years prior to presentation.

Family history was notable for a sister with multiple sclerosis.

On review of systems, the patient noted occasional pain in her right knee.

At the time of presentation, her medications were:

- Dilantin 200 mg per day
- Synthroid 0.125 mg
- B12 by monthly injection
- Tobradex drops bid OU

Examination on first presentation revealed best corrected visual acuity of 20/50 in the right eye and 20/40 in the left. On slit lamp examination, there was slight meibomian gland dysfunction and blepharitis bilaterally. There were occluded lacrimal puncta, mild conjunctival injection, fornix foreshortening and symblepharon bilaterally. The anterior chambers were deep and quiet. The irides and pupils were unremarkable. Both lenses showed mild nuclear sclerosis. The vitreous bodies were clear. Fundoscopic exam was unremarkable in both eyes. Intraocular pressures were normal bilaterally.

These are photographs of the patient at the first presentation.
It should be noted that an antineutrophil cytoplasmic autoantibodies (ANCA) assay done in April of 1993, which was a year before her first visit, was positive for perinuclear staining (pANCA) and a positive ELISA confirmed the presence of antibodies to myeloperoxidase (MPO).

In light of these findings, the impression at this presentation was cicatrizing conjunctivitis OU.

Conjunctival biopsy from the right eye was performed and blood was sent for complete blood count (CBC), antinuclear antibodies (ANA), glucose 6 phosphate dehydrogenase (G6PD), liver function test (LFT) and Lyme titers.

The patient returned 2 weeks later (11/08/94), feeling subjectively the same. The examination was the same except for slightly increased conjunctival injection.

The lab results were significant for ANA (both rat liver and hep 2 substrate were positive at 1:640 homogenous pattern). Antibody to double stranded DNA was moderately positive. ANCA was negative. Slightly elevated Alkaline phosphatase was noted. Conjunctival biopsy demonstrated C4 deposition at the basement membrane zone (BMZ).

The diagnosis was ocular cicatricial pemphigoid (OCP) stage 3 and Dapsone 25 mg twice daily was started.

On the next follow up (12/22/94), the patient was subjectively better. Her exam showed 1+ conjunctival injection. Dapsone was increased to 100 mg per day.

Three weeks later (1/12/95), conjunctival injection improved but still active. Her hematocrit (Hct) slightly dropped and reticulocyte count rose to 2%. At this point, the decision was made to plan on stopping Dapsone and starting MTX but this change was withheld pending consultation with her internist.

At the next follow up 6 wks later (3/02/95), the patient reported increased seizure activity. The exam showed slight conjunctival injection. CBC and reticulocyte count were normal. Dapsone was maintained and MTX was not initiated.

Two months later (5/09/95), the patient showed evidence of chronic blepharitis bilaterally and was instructed on lid care. The cicatricial pemphigoid was inactive. She was on Prednisone taper for polyarthritis.

Three months later (8/08/95), her blepharitis was still active. Doxycycline 100 mg daily was prescribed.
Two weeks later (8/22/95), the patient had arthritis in her knees, right MCP joints and right wrist. She had fluid aspiration from her left knee and local steroids injection by a rheumatologist. Persistent significant oral ulcers were noted. Medications were the same.

A month later (9/18/95), oral ulcers still persisted with burning sensation. Imuran was started at 100 mg daily.

These are pictures of the mouth lesions:

![Mouth Lesions]

Repeated lab results were significant for:

- pANCA
- ELISA was positive for anti MPO antibodies.
- Raji cell assay was positive
- repeated ANA titer was negative and the complements were normal.

Nine weeks later (11/27/95), the patient continued to have oral ulcers which were biopsied by a dermatologist. The result could not distinguish pemphigoid or lichen planus.

A month later (12/28/95), her rheumatologist had discontinued Imuran as it didn't appear effective against the oral lesions.

Oral Prednisone was increased to 50 mg daily.

Four weeks later (1/25/96), the patient's oral ulcer worsened and repeat oral biopsy revealed lichen planus. Her eye condition remained stable.

2% CsA solution swish was prescribed and Prednisone was tapered and discontinued.

Five month later (6/19/96), a third oral biopsy confirmed the diagnosis of lichen planus. Eyes remained stable and Dapsone was discontinued.

Two month later (8/14/96), the oral lesions were less bothersome. The eyes were quiet. The patient was offered Plaquinil but refused.

The lab results were negative for ANA, ANCA and rheumatoid factor (RF).
These pictures showed the improvement of the mouth lesions:

These are the patient's eyes.

DISCUSSION

This case reveals to us the scenario of multiple autoimmune diseases. The history of recurrent cicatrizising conjunctivitis along with strongly positive compliment deposition at the level of conjunctival BMZ make a definite diagnosis of OCP.

However, this patient also presents with the problem of recurrent painful lesions at the tongue and buccal mucosa. The review of systems doesn't show any dermatologic problem other than her oral lesions. Oral mucosal biopsy was repeated until the final result revealed lichen planus. Past medical history revealed hypothyroidism and recurrent polyarthritis plus +ANA and +pANCA. However, other clinical findings and lab results are not enough to make a definite diagnosis of SLE, rheumatoid arthritis or other form of ANCA associated vasculitis.

OCP and lichen planus will be described briefly, just to give you the overview of these two autoimmune diseases. The association of multiple immune diseases will be discussed later.

OCULAR CICATRICIAL PEMPHIGOID

INTRODUCTION

Ocular cicatricial pemphigoid is a systemic autoimmune disease with both ocular and nonocular manifestations. It produces scarring of the affected skin, conjunctiva and other mucous membrane. Conjunctival involvement may occur as early as 10 years before other mucosal or skin lesion develop or the disease can be limited to the conjunctiva. This disease can be fatal when stricture from scarring in the esophagus or trachea developed.
EPIDEMIOLOGY

The estimated prevalence of this disease is 1 in 15,000 (Bittelheim) to 1 in 20,000 (Hardy and Lamb). However, the earliest stage of the disease is usually underrecognized. This disease has a slight female preponderance with a female to male ratio of 2:1. It has a worldwide distribution and effects all races. CP is said to be a disease of the elderly with the average age of 65 but this figure are probably under reported because the cases are usually not in their earliest stages. However, this disease can begin as early as the third decade of life as well.

PATHOGENESIS

OCP is an autoimmune disease and is believed to result from a type 2 hypersensitivity with a genetic predisposition and environmental factors to trigger the onset of the disease. The susceptibility gene is at or closely linked to the HLA-DQw7 gene. Individuals carrying this gene have approximately 9.6 relative risk of developing OCP. The environmental trigger that stimulates the individual to develop OCP may be microbial or chemical.

Drug induced OCP can be associated with

Practolol Pilocarpine Timolol Echothiophate iodide Epinephrine

HISTOLOGY AND IMMUNOPATHOLOGY

Pemphigoid is characterized by a separation of basal epithelium from underlying basement membrane, forming a subepithelial bleb that tend to form scar.

The histopathologic finding of the conjunctiva in OCP patients shows: submucosal scarring, chronic inflammation, perivasculitis, squamous metaplasia of the epithelium with loss of goblet cells.

Immunohistochemical staining shows predominantly CD4 helper T lymphocytes in the inflammatory cell population that develops in the substantia propria.

Immunoglobulins and complement components are present in the epithelial basement membrane zone of the conjunctiva which was used as a definitive diagnosis for OCP. This can be detected by either Immunofluorescence or Immunoperoxidase method which is much more sensitive. Circulating autoantibodies to the basement membrane are found in all of these patients when radioimmunoassay techniques are employed. Circulating antibodies to conjunctival epithelium have been detected. The idiopathic OCP antigen is definitely different from those of pemphigoid and drug induced OCP. This antigen is a 205-kd protein in the lamina lucida of the BMZ.

This is the picture of positive immunofluorescence staining showing a linear deposition of Ig on the conjunctival BMZ.
The immunopathologic abnormalities are not restricted to the eye. Systemic immunologic derangements are present as well, including

- slightly abnormal proportions of circulating helper T cells
- evidence of systemic immunoreactivity with elevated levels of sIL-2R
- elevated levels of soluble CD 8 glycoprotein
- elevated levels of TNF in the serum.

Circulating autoantibodies against pancreas, thyroid and adrenal gland have been detected (Yarian). ANA can be found in 67% of OCP patients.

MANIFESTATION

OCULAR:

Ocular manifestation in CP usually begins as a unilateral conjunctivitis which is chronic in nature. It's usually a bilateral disease but markedly asymmetrical and is not uncommon to find the disease just only in one eye. Four stages of OCP have been described as follow:

Stage 1 is characterized by chronic conjunctivitis with mild conjunctival or corneal epitheliopathy and subepithelial fibrosis of the conjunctiva. The fibrosis is best seen at the tarsal conjunctiva as fine white striae.

Stage 2 is characterized by cicatrizing process with fornix foreshortening.

Stage 3 is when symblepharon occurred.

Stage 4 which is the end stage, consists of a dry eye with keratinization of the cornea and ankyloblepharon. This stage is untreatable.

With the appearance of the secondary trichiasis and tear film abnormalities, the blinding consequences are corneal epitheliopathy, secondary infection and corneal neovascularization.

EXTRAOCULAR:

The nonocular manifestations include skin, scalp, oral mucosa, nasal mucosa, pharynx, larynx, trachea, esophagus, vagina, urethra and anus. Scarring of the skin and mucosa is usual. The desquamative gingivitis presents in nearly all patients. Skin lesions can manifest as either a
recurrent vesicobullous lesions or an erythematous plaques which evolve into a pruritic blisters.

DIAGNOSIS

Differential diagnosis of cicatrizing conjunctivitis

cicatricial pemphigoid intraepithelial epithelioma

atopic keratoconjunctivitis Stevens-Johnson syndrome

Ocular rosacea Lyell's syndrome

Scleroderma Sarcoidosis

Corynebacterium diphtheriae Trachoma

conjunctivitis Adenovirus conjunctivitis

Chemical burn Trauma

Squamous cell carcinoma Sebaceous cell carcinoma

Epidermolysis bullosa acquisita Sjogren syndrome

Dermatitis herpetiformis Erythoderma ichthyosiform congenita

Porphyria cutanea tarda Pemphigus vulgaris

Many diseases from this differential diagnosis can be excluded on the basis of history and physical examination. The definitive diagnosis of OCP requires the demonstration of immunoglobulin or complement component deposition at the epithelial BMZ of the biopsied conjunctiva.

TREATMENT

OCP is a systemic autoimmune disease and should be treated systemically in collaboration with the chemotherapist or rheumatologist. Current chemotherapeutic agents are as shown in the slide. Detail of the treatment will not be discussed here.

Therapy for ocular cicatricial pemphigoid

Agent Initial Dose/ Maximal Dose

Dapsone 25 mg bid /150 mg/day

Methotrexate 7.5 mg once weekly/ 15 mg once weekly

Azathioprine 2 mg/kg/day/ 3 mg/kg/day

Cyclophosphamide 2 mg/kg/day/ 3 mg/kg/day
LICHEN PLANUS

The next disease that will be discussed is lichen planus which is usually a unique cutaneous entity consisting of an eruption of papules with distinct color and configuration.

EPIDEMIOLOGY

The incidence of LP appears to vary slightly among geographic area. The disease was found in 0.44 percent of the dermatologic patients in United State and 0.14 percent in Palestine. No racial or definite sexual predilection has been noted.

Most of the affected are between the age of 30 and 60. Although no age group is exempt, the disease is uncommon in the extreme age groups.

ETIOLOGY AND PATHOGENESIS

The cause of lichen planus remains unknown. Chemical agents as listed in the slide can induce LP in certain persons. A cell-mediated immune reaction may be involved in the pathogenesis of this disease.

Agents reported to induce cutaneous disorders that resemble typical lichen planus

- Antiarthritic Gold
- Antibiotic Streptomycin Tetracycline
- Antiluetic Arsenic Mercury Iodides
- Antimalarial Chloroquin Quinidine Quinine
- Antitubercular Para-aminosalicylic acid
- Ataraxis Phenothiazines derivative
- Chelator Penicillamine
- Color-film developer p-Phenylenediamine salts
- 2-amino-5-diethylamino-toluene CI (CD2)
- 4-amino-n-diethyl-aniline sulfate (TTS)
- Antimony trioxide
- Diuretic Thiazides
MANIFESTATIONS

The physical signs of lichen planus are usually found on the skin and mucous membranes. There are a wide array of variants but the classic skin lesion is a tiny, violaceous, flat-topped, polygonal, glistening papule with or without central umbilication. Lesions are usually symmetrical and on the flexor surfaces of the forearms, neck, thighs, chin and lower back. Koebner phenomenon can occur. Lichen planus may exhibit numerous variations as shown here:

Variations of pattern in lichen planus

1. Difference in configuration
   - Annular
   - Linear

2. Difference in site
   - Mucous membrane
   - Genitalia
   - Nails
   - Scalp

3. Difference in morphology
   - Hypertrophic Actinicus
   - Follicular Erythematous
   - Vesicular and bullous Exfoliative
   - Erosive and ulcerative
   - Atrophic

Malignant degeneration

only mucous membrane involvement will be described. The area of highest incidence is the buccal mucosa; lesions are also found on the tongue, lips, gum, palate, pharynx and throughout the gastrointestinal tract. The vaginal mucosa, bladder, larynx, and conjunctiva also may be affected. Mucous membrane lesions occur in about two-thirds of all cases and in 15 to 25 percent of cases they may be the only manifestation. There is often a reticulated or lacelike network of linear, white or gray striae. Lesions are asymptomatic or may have some burning sensation. However, when chronic erosions are present, the lesions may become extremely painful as seen in our patient.
HISTOLOGY AND IMMUNOPATHOLOGY

Histology shows degeneration of the basal cell layer and mononuclear cell mostly helper T cells infiltrate in the upper dermis and dermo-epidermal junction. Hyperkeratosis is prominent. Eosinophilic bodies called colloid bodies are often found in the lower part of the rete ridges and at the basement membrane zone. This finding may be an example of apoptosis.

There are characteristic immunofluorescent findings that are suggestive but not diagnostic of LP. The subepidermal and intraepidermal colloidal bodies contain IgM and/or IgA, IgG, C3, and fibrin. Fibrin deposition occurred in a broad band pattern along the BMZ and at the dermo-epidermal junction of the skin and buccal mucosa. Granular basement membrane deposits of IgM and IgG have been reported. The conjunctiva showed multilamellar fragmented BMZ.

DIAGNOSIS

Typical lesion is sufficient to make a clinical diagnosis. Histopathology and immunofluorescent findings will confirm the diagnosis or establish the diagnosis in an atypical case. In our case the differential diagnosis for oral lesions are as followed:

Differential diagnosis for mucous membrane lesion

Mucous membrane pemphigoid
Lichen planus
Erythema multiform
Leukoplakia
Candidiasis
Lupus erythematosus
Secondary syphilis

In this case, the presence of chronic, atypical oral ulceration demands repeated biopsies to make a definitive diagnosis which was very helpful in giving the treatment.

TREATMENT

Numerous regimens have been used: heavy metals (arsenic, mercury, bismuth), antibiotics (penicillin, broad-spectrum drugs), vaccines, antimalarials, antituberculous, calcium gluconate, physical therapy (x-ray, UV) and vitamins. There are no well-controlled studies conforming the effectiveness of the various regimens. The variable course and self-limited duration of the disease make it difficult to adequately evaluate therapy.

Corticosteroids are useful in the treatment of lichen planus. Topical application is usually effective for typical skin lesions. Systemic administration of a 2 to 6 week course of oral steroids will relief the symptoms in most cases. Oral lesion may be treated with topical steroid in Orabase or intralesional injection in the resistant case. Tretinoin in Orabase, 2% CsA swish and betamethasone in aerosol applied topically has been found to be effective.
MULTIPLE AUTOIMMUNE DISORDERS

INTRODUCTION

Disorders of autoimmune pathogenesis occur with increased frequency in patients with previous history of another autoimmune disease. The tendency to develop another disease occurs in about 25% of these patients. Overlapping sometimes occurs but commonly it is the time that allow one syndrome to take on the features of another.

DEFINITION

Several efforts have been made to group and label these coexisting autoimmune disorders. The term Overlap Syndromes has been used to describe the group of patients exhibit features of more than one established autoimmune disorders. Several combinations of definite connective tissue diseases have been reported.

Undifferentiated connective tissue disease (UCTS) is used for patients who have features strongly suggestive of connective tissue disease but not definitely diagnostic of any one disorder.

Mixed connective tissue disease (MCTD) was initially described by Sharp as a new syndrome with features of systemic lupus erythematosus (SLE), systemic sclerosis, polymyositis and rheumatoid arthritis and high titers of circulating antibody to nuclear ribonucleoprotein (RNP) antigen.

It should be noted that the classification of overlap, UCTS and MCTD is based on descriptive phenomena. This classification usually has only a loose statistical relationship with prognosis and outcome and is frequently confusing when applied to the individual patient.

Multiple autoimmune syndromes (MAS) is the combination of at least three autoimmune diseases in the same patient. This new classification based on 91 reported cases of morbid associations concerns the grouping of autoimmune conditions in the same patient.

Classification of MAS

Type 1 Myasthenia gravis
Thymoma
Polymyositis
Giant cell myocarditis
Type 2 Sjögren's syndrome
Rheumatoid arthritis
Primary biliary cirrhosis
Scleroderma
Autoimmune thyroid disease
Type 3 Autoimmune thyroid disease
Myasthenia gravis and/or thymoma
Sjögren's syndrome
Pernicious anemia
Idiopathic thrombocytopenic purpura
Addison's disease
Diabetes mellitus
Vitiligo
Autoimmune hemolytic anemia
Lupus erythematosus
Dermatitis herpetiformis

Criteria: at least three conditions must be present in the same patient

Conditions found in various combinations in MAS

Type 1 Pemphigus
Autoimmune thyroid disease
Type 2 Chronic active hepatitis
Lupus erythematosus
Pemphigus
Bullous pemphigoid
Autoimmune hemolytic anemia
Idiopathic thrombocytopenic purpura
Alopecia areata
Addison's disease
Type 3 Acquired primary hypogonadism
Hypophysitis
Rheumatoid arthritis
Primary biliary cirrhosis
Relapsing polychondritis
Multiple sclerosis
Chronic active hepatitis
Ulcerative colitis
Scleroderma

This system of classification is of particular interest. Firstly, it should make research and analysis of these morbid associations easier. Secondly, it offers the possibility of foreseeing and detecting a new condition liable to appear in a patient who has had two previous autoimmune diseases. Finally, it provides a new basis of analysis for the pathophysiological mechanisms of autoimmunity.

PATHOGENESIS

The pathogenesis of multiple autoimmune disorders is still unknown. Environmental triggers in a genetically susceptible individual are believed to cause disorders of immune regulation. As supported by the animal experiment which shows multiple autoantibodies following CMV infection. Multiple autoantibodies can be found in one patient and some of the specific mono or polyclonal autoantibodies may be multiple organs reactive.

CLINICAL MANIFESTATION

Clinical manifestations depend on the combination of the autoimmune disorders but are usually nonspecific.

DIAGNOSIS

When establishing the diagnosis of multiple autoimmune diseases, the diagnosis of each component disease follows its own independent criteria.

CONCLUSION

The presence of one autoimmune disease should alert the physician to watch for the second immunologic disorder. Finding inconsistent with one’s original diagnosis merit the search for a second autoimmune condition. The case presented here highlights the need for awareness of the possibility of multiple autoimmune phenomena. The occurrence of multiple autoimmune phenomena in this case indicates the need for continued surveillance for the development of new autoimmune disease in predisposed patients.

QUESTIONS FOR MULTIPLE AUTOIMMUNE DISEASES

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1. Which of the following statements regarding multiple autoimmune diseases is not correct?

a. For a patient with an autoimmune disease, the likelihood of developing a second autoimmune disease is 50%.
b. Multiple autoimmune syndrome is the combination of at least three autoimmune diseases in the same patient.
c. Overlap syndrome is a term used for patients who have more than one established autoimmune disease.
d. Mixed connective tissue disease is a syndrome with features of SLE, systemic sclerosis, polymyositis and rheumatoid arthritis.

2. Which of the following statements regarding the epidemiology of ocular cicatricial pemphigoid is incorrect?

a. OCP has a female preponderance.
b. The estimated prevalence is 1 in 15,000 to 1 in 20,000.
c. This disease has a worldwide distribution and affects all races.
d. OCP is a disease of the middle age with the average age of onset at 40 years.

3. Which of the following medications has not been associated with drug induced OCP?

a. Atropine  
b. Pilocarpine  
c. Timolol  
d. Epinephrine

4. What is the characteristic immunopathology of OCP?

a. Immunoglobulins and complement components are present in the epithelial basement membrane zone of the conjunctiva.  
b. Immunofluorescence staining shows immunoglobulin deposition in the conjunctival stroma.  
c. Colloid bodies are often found in the subepithelial region.  
d. Fibrin deposition is found along the basement membrane zone of the conjunctiva.

5. Which of the following statements regarding the immunopathology of OCP is not correct?

a. Circulating autoantibodies to conjunctival basement membrane are seldom found in OCP patients.  
b. ANA can be positive in 67% of OCP patients.  
c. Circulating autoantibodies to thyroid and adrenal gland can be detected in OCP patients.  
d. Serum interleukin 2 receptor (sIL-2R) can be elevated in OCP patients.

6. Which of the following statements is incorrect regarding the ocular manifestations of OCP?

a. OCP is usually bilateral.  
b. The subepithelial fibrosis in OCP can be best demonstrated in the tarsal conjunctiva as fine
white striae.
c. Stage 2 of OCP is characterized by fornix foreshortening.
d. Stage 3 of OCP is the untreatable end stage.

7. What is the most serious sign/symptom that physicians need to be aware of when treating OCP patients?

a. Chronic eye irritation.
b. Gingivitis.
c. Pruritic blisters at the skin.
d. Dysphagia.

8. Which of the following statements is incorrect regarding the treatment of OCP?

a. Treatment usually begins with systemic Dapsone 25 mg twice daily in a mild case.
b. The early stage of OCP can be treated with topical immunosuppressive agents alone.
c. Secondary trichiasis and tear film abnormalities should be treated.
d. Keratoplasty in OCP patients has a low probability of success.

9. Which of the following findings is not characteristic of lichen planus?

a. A violaceous, flat-topped, polygonal papule on the skin.
b. Papules are usually on the extensor surfaces of the forearms, neck, thighs, chin and lower back.
c. Lesions are usually symmetrical.
d. Mucous membrane lesions occur in about two-thirds of all cases.

10. Which of the following findings is not an immunopathologic characteristic of lichen planus?

a. Subepidermal and intraepidermal colloid bodies.
b. Broad band fibrin deposition along the basement membrane zone.
c. Multilamellar fragmented conjunctival basement membrane.
d. Generalized deposition of complement components at the dermoepidermal junction.

ANSWERS TO MULTIPLE AUTOIMMUNE DISEASE QUESTIONS

1. a.
The likelihood of developing a second autoimmune disease is 20% in this type of patients.


2. d

OCP is a disease of the elderly with an average age of onset of 60 years.


3. a
Pilocarpine, Timolol and Epinephrine, except Atropine, have all been associated with drug induced OCP.


4. a


5. a

The autoantibodies in patients with OCP can be detected in all patients when the disease is active.


6. d

Stage III OCP characterized by symblepharon formation and is neither the untreatable nor the end stage of the disease.


7. d

OCP can be fatal if tracheal or esophageal strictures occur.


8. b

OCP is a systemic disease and should be treated systemically. Details of the treatment modalities can be found in the provided reference below or any standard ophthalmology textbooks.


9. b

Lesions usually occur on the flexor surfaces of the forearms, neck, thighs, chin and lower back.


10 .d

a-c are all correct concerning the immunopathology of lichen planus.