# Oral Pathology

Lecture

## Immune-Mediated disorders

### Recurrent aphthus stomatitis

**Etiology:** Although the cause of aphthous ulcerations is unknown, several possibilities have been postulated

There is considerable evidence that aphthous ulcers are related to a focal immune dysfunction in which T lymphocytes have a significant role.

Deficiencies of vitamin B12, folic acid, and iron as measured in serum have been found in only a small percentage of patients with aphthous ulcers. Correction of these deficiencies has produced improvement or cure in this small group. Patients with malabsorption conditions such as celiac disease (gluten-sensitive enteropathy or nontropical sprue) and Crohn's disease have been reported as having occasional aphthous-type ulcers, with the latter disease possibly related to an auto inflammatory process. In such cases, deficiencies of folic acid and factors related to underlying disease may be part of the cause.

**Clinical Features.** Three forms of aphthous ulcers have been recognized: **minor, major, and herpetiform aphthous ulcers**. All are believed to be part of the same disease spectrum, and all are believed to have a common etiology. Differences are essentially clinical and correspond to the degree of severity. All forms present as painful recurrent ulcers. Patients occasionally have prodromal symptoms of tingling or burning before the appearance of lesions. The ulcers are not preceded by vesicles and characteristically appear on the vestibular and buccal mucosa, tongue, soft

palate, fauces, and floor of mouth. Only rarely do these lesions occur on the attached gingiva and hard palate, thus providing an important clinical sign for the separation of aphthous ulcers from secondary herpetic ulcers. In patients with AIDS, however, aphthous-like ulcers may occur at any mucosal site.

**Minor Aphthous Ulcers.** Minor aphthous ulcers are the most commonly encountered form. This type usually appears as a single, painful, oval ulcer that is less than 0.5 cm in diameter, covered by a yellow fibrinous membrane and surrounded by an erythematous halo. Multiple oral aphthae may be seen. When the lateral or ventral surfaces of the tongue are affected, pain tends to be out of proportion to the size of the lesion. Minor aphthous ulcers generally last 7 to 10 days and heal without scar formation. Recurrences vary from one individual to another. Periods of freedom from disease may range from a matter of weeks to as long as years.

In some patients with reluctant aphthae, a diagnosis of Crohn's disease may be considered. This granulomatous disease may affect the gastrointestinal tract from mouth to anus. Oral manifestations include mucosal fissures and small, multiple, hyperplastic nodules on the buccal mucosa, producing a cobblestone appearance. Biopsy findings of these mucosal nodules show small, noncaseating granulomas characteristic of Crohn's disease. HIV-positive patients may develop minor aphthous ulcers, although proportionately more have major or herpetiform lesions.

**Major Aphthous Ulcers.** Major aphthous ulcers were previously thought to be a separate entity, and this form was referred to as periadenitis mucosa necrotica recurrens or Sutton's disease. It is now regarded as the most severe expression of aphthous stomatitis. Lesions are larger (>0.5 cm) and more painful and persist longer than minor aphthae. Because of the depth

of inflammation, major aphthous ulcers appear crateriform clinically and heal with scar formation. Lesions may take as long as 6 weeks to heal, and as soon as one ulcer disappears, another one starts. In patients who experience an unremitting course with significant pain and discomfort, systemic health may be compromised because of difficulty in eating and psychological stress. The predilection for movable oral mucosa is as typical for major aphthous ulcers as it is for minor aphthae. HIV-positive patients may have aphthous lesions at any intraoral site.

**Herpetiform Aphthous Ulcers.** Herpetiform aphthous ulcers present clinically as recurrent crops of small ulcers. Although movable mucosa is predominantly affected, palatal and gingival mucosa may also be involved. Pain may be considerable, and healing generally occurs in 1 to 2 weeks. Unlike herpes infection, herpetiform aphthous ulcers are not preceded by vesicles and exhibit no virus-infected cells. Other than the clinical feature of crops of oral ulcers, no finding can link this disease to a viral infection.

## Histopathology

Because the diagnosis of these ulcers is usually evident clinically, biopsies usually are unnecessary and therefore are rarely performed. Aphthous ulcers have nonspecific microscopic findings, and no histologic features are diagnostic. At no time are virus-infected cells evident. Essentially, the same microscopic changes are found in all forms of aphthous ulcers. Studies have shown that mononuclear cells are found in submucosa and perivascular tissues in the preulcerative stage. These cells are predominantly CD4 lymphocytes, which soon are outnumbered by CD8 lymphocytes as the ulcerative stage develops. Macrophages and mast cells are common inhabitants of the ulcer.

**Treatment:** In patients with occasional or few minor aphthous ulcers,

usually no treatment is needed apart from a bland mouth rinse such as sodium bicarbonate in warm water to keep the mouth clean. However, when patients are more severely affected, some forms of treatment can provide significant control (but not necessarily a cure) of this disease.

Rational treatment would include drugs that can manipulate or regulate immune responses. In this category, corticosteroids currently offer the best chance for disease containment. In severely affected patients, systemic steroids may be used for immediate control.

Although nearly all topical compounds have been developed for use on the skin, it has been standard practice to prescribe these agents for use on mucous membranes. Intralesional injection of triamcinolone may be used for individual or focal problematic lesions.

## Behçet's Syndrome

Behçet's syndrome is a rare multisystem inflammatory disease (gastrointestinal, cardiovascular, ocular, CNS, articular, pulmonary, dermal) in which recurrent oral aphthae are a consistent feature. Although the oral manifestations are usually relatively minor, involvement of other sites, especially the eyes and CNS, can be serious.

**Clinical Features.** Lesions of Behçet's syndrome typically affect the oral cavity (100% incidence), the genitalia (62% of cases), and the eyes. Other regions or systems are less commonly involved. Recurrent arthritis of the wrists, ankles, and knees may be associated. Cardiovascular manifestations are believed to result from vasculitis and thrombosis. CNS manifestations are frequently seen in the form of headaches, although infarcts have been reported.

Oral manifestations of this syndrome appear identical to the ulcers of

aphthous stomatitis. The ulcers are usually the minor aphthous form and are found in the typical aphthous distribution.

Ocular changes are noted in most patients with Behçet's syndrome. Uveitis, conjunctivitis, and retinitis are among the more common inflammatory processes.

Genital lesions are ulcerative in nature and may cause significant pain and discomfort. Painful ulcerative lesions may occur around the anus. Inflammatory bowel disease and neurologic problems have been described in some patients.

Histopathology.

T lymphocytes are prominent in the ulcerative lesions of Behçet's syndrome. However, neutrophilic infiltrates in which the cells appear within vessel walls (vasculitis) have been described. Immunopathologic support of a vascular target in this condition comes from the demonstration of immunoglobulins and complement within the vessel walls.

Diagnosis. The diagnosis of Behçet's syndrome is based on clinical signs and symptoms associated with the various regions affected. No specific findings are noted in biopsy tissue, and no supportive laboratory tests are available.

Treatment. No standard therapy is known for Behçet's syndrome. Systemic steroids are often prescribed

Immunosuppressive drugs, such as chlorambucil and azathioprine, may be used instead of or in addition to steroids. Dapsone, cyclosporine, thalidomide, interferon, and biological anti–tumor necrosis factor (TNF) agents may play a role in the treatment of these patients, depending on the degree of disease severity.

# Mucosal and Skin Condition:

## LICHEN PLANUS

Lichen planus is a relatively common, chronic dermatologic disease that often affects the oral mucosa. The strange name of the condition was provided by the British physician Erasmus Wilson, who first described it in 1869. Lichens are primitive plants composed of symbiotic algae and fungi. The term planus is Lat in for " flat. " Wilson probably thought that the skin lesions looked similar enough to the lichens growing on rocks to merit this designation.

A variety of medications may induce lesions that appear clinically identical to the idiopathic form of the condition: however, the term lichenoid mucositis (or lichenoid dermatitis, depending on the site involved) is probably a better name for the drug- related alterations. Similarly, foreign material that becomes inadvertently embedded in the gingiva may elicit a host response that is termed lichenoid foreign-body gingivitis.

Clinical Features

Most patient s with lichen planus are middle-aged adults. It is rare for children to be affected .Women predominate in most series of cases, usually by a 3:2 ratio over men. approximately 1% of the population may have cutaneous lichen planus. The prevalence of oral lichen planus is between 0. 1% and 2.2%. The skin lesions of lichen plan us have been classically described as purple, pruritic, polygonal papules. These usually affect the flex or surfaces of the extremities. Excoriations may not be visible. despite the fact that the lesions itch , because it hurts the patient

when he or she scratches them. Careful examination of the surface of the skin papules reveals a fine, lacelike network of white lines (Wickham's striae). Other sites of extraoral involvement include the glans penis the vulvar mucosa, and the nails Essentially there are two forms of oral lesions: (1) reticular and (2) erosive. Reticular lichen planus. Reticular lichen planus is much more common than the erosive form, but the erosive form predominates in several studies. This is probably because of referral bias (because the erosive form is symptomatic).The reticular form usually causes no symptoms and involves the posterior buccal mucosa bilaterally. Other oral mucosal surfaces may also be involved concurrently, such as the lateral and dorsal tongue, the gingivae, the palate, and vermilion border.

Reticular lichen planus is thus named because of its characteristic pattern of interlacing white lines (also referred to as Wickham's striae); however, the white lesions may appear as papules in some instances, These lesions are typically not static but wax and wane over weeks or months, The reticular pattern may not be as evident in some sites, such as the dorsal tongue where the lesions appear more as keratotic plaques with atrophy of the papillae.

Erosive lichen planus, although not as common as the reticular form is more significant for the patient because the lesions are usually symptomatic. Clinically, there are atrophic, erythematous areas with central ulceration of varying degrees. The periphery of the atrophic regions is usually bordered by fine, white radiating striae. Sometimes the atrophy and ulceration are confined to the gingival mucosa, producing the reaction pattern called desquamative gingivitis. In such cases, biopsy specimens should be obtained for light microscopic and immunofluorescent studies of perilesional tissue, because cicatricial pemphigoid and pemphigus vulgaris may appear in a similar fashion. If the erosive component is severe,

epithelial separation may occur. This results in the relatively rare presentation of bullous lichen planus.

Histopathologic Features

The histopathologic features of lichen planus are characteristic but may not be specific because other conditions such as lichenoid drug reaction, lichenoid amalgam reaction, lupus erythematosus, chronic ulcerative stomatitis, and oral mucosal cinnamon reaction may also show a similar histopathologic pattern. Varying degrees of orthokeratosis and parakeratosis may be present on the surface of the epithelium, depending on whether the biopsy specimen is taken from an erosive or reticular lesion.

The thickness of the spinous layer can also vary. The reteridges may be absent or hyperplastic, but they classically have a pointed or "saw toothed" shape. Destruction of the basal cell layer of the epithelium (hydropic degeneration) is also evident. This is accompanied by an intense, band like infiltrate of predominantly T-lymphocytes immediately subjacent to the epithelium. Degenerating keratinocytes may be seen in the area of the epithelium and connective tissue interface and have been termed colloid, cytoid, hyaline, or Civatte bodies.

No significant degree of epithelial atypia is expected in oral lichen planus although lesions having a superimposed candidal infection may appear worrisome. These should be reevaluated histopathologically after the candidal infection is treated.

The immunopathologic features of lichen planus are non specific. Most lesions show the deposition of a shaggy band of fibrinogen at the basement membrane zone.

Treatment and Prognosis

Reticular lichen planus typically produces no symptoms and no treatment is needed. Occasionally; Affected patients may have superimposed candidiasis. in which case they may complain of a burning sensation of the oral mucosa. Antifungal therapy is necessary in such a case. Some investigators recommend annual reevaluation of the reticular lesions of oral lichen planus.

Erosive lichen planus is often bothersome because of the open sores in the mouth because it is an immunologically mediated condition. corticosteroids are recommended. The lesions respond to systemic corticosteroids, but such drastic therapy is usually not necessary. One of the stronger topical corticosteroids (e.g.• Iluoclnonlde, betamethasone. clobetasol gel) applied several times per day to the most symptomatic areas is usually sufficient to induce healing within I or 2 weeks.

## Erythema Multiforme

(EM) is an acute self-limiting hypersensitivity reaction characterized by target skin lesions and/or ulcerative oral lesions. It has been divided into two subtypes: a minor form, usually associated with an HSV trigger, and a major severe form, triggered by certain systemic drugs.

**Etiology and Pathogenesis.**

The basic cause of EM is unknown, although a hypersensitivity reaction is suspected. Some evidence suggests that the disease mechanism may be related to antigen-antibody complexes that are targeted for small vessels in the skin or mucosa. In about half of cases, precipitating or triggering factors can be identified. These generally fall into the two large categories

of infections and drugs. Other factors, such as malignancy, vaccination, autoimmune disease, and radiotherapy, are occasionally cited as possible triggers. Infections frequently reported include HSV infection (due to HSV types 1 and 2), TB, and histoplasmosis.

## Clinical Features

EM is usually an acute, self-limited process that affects the skin or mucous membranes or both. Between 25% and 50% of patients with cutaneous EM have oral manifestations of this disease. It may on occasion be chronic, or it may be a recurring acute problem. In recurrent disease, prodromal symptoms may be experienced before any eruption. Young adults are most commonly affected. Individuals often develop EM in the spring or fall. The term erythema multiforme was coined to indicate the multiple and varied clinical appearances that are associated with cutaneous manifestations of this disease.

The classic skin lesion of EM is the target or iris lesion. It consists of concentric erythematous rings separated by rings of near-normal color. Typically, the extremities are involved, usually in a symmetric distribution. Other types of skin manifestations of EM include macules, papules, vesicles, bullae, and urticarial plaques.

Orally, EM characteristically presents as an ulcerative disease, varying from a few aphthous-type lesions to multiple superficial, widespread ulcers in EM major. Short-lived vesicles or bullae are infrequently seen at initial presentation. Any area of the mouth may be involved, with the lips, buccal mucosa, palate, and tongue being most frequently affected. Recurrent oral lesions may appear as multiple painful ulcers similar to those of the initial episode or as less symptomatic erythematous patches with limited ulceration

Symptoms range from mild discomfort to severe pain. Considerable apprehension may be associated with this condition initially because of occasional explosive onset in some patients. Systemic signs and symptoms of headache, slightly elevated temperature, and lymphadenopathy may accompany more intense disease.

At the severe end of the EM spectrum (EM major), intense involvement of the mouth, eyes, skin, genitalia, and occasionally the esophagus and respiratory tract may be seen concurrently. This form of EM major, sometimes called Stevens-Johnson syndrome, has a strong relationship to medications, in particular analgesics, where oxicams or propionic acid derivatives have been used

Characteristically, the lips show crusting ulceration at the vermilion border that may cause pain. Superficial ulceration, often preceded by bullae, is common to all sites affected. Ocular inflammation (conjunctivitis and uveitis) may lead to scarring and blindness.

## Histopathology.

The microscopic pattern of EM consists of epithelial hyperplasia and spongiosis. Basal and parabasal apoptotic keratinocytes are usually seen. Vesicles occur at the epithelium–connective tissue interface, although intraepithelial vesiculation may be seen. Epithelial necrosis is a frequent finding. Connective tissue changes usually appear as infiltrates of lymphocytes and macrophages in perivascular spaces and in connective tissue papillae.

## Treatment

In EM minor, symptomatic treatment, including keeping the mouth clean with bland mouth rinses, may be all that is necessary. In EM major, topical

corticosteroids with antifungals may help control disease. The use of systemic corticosteroids remains controversial and is believed by some to be contraindicated,particularly as maintenance therapy. Acyclovir at 400 to 600 mg daily may be effective in preventing recurrences in patients who have an HSV-triggered disease, although the efficacy is not clear. Supportive measures, such as oral irrigation, adequate fluid intake, and use of antipyretics, may provide patients with substantial benefit.

## LUPUS ERYTHEMATOSUS

Lupus erythematosus (LE) is a classic example of an immunologically mediated condition, and is the most common of the so-called "collagen vascular" or "connective tissue". It may exhibit any one of several clinicopathologic forms. Systemic lupus erythematosus (SLE) is a serious multisystem disease with a variety of cutaneous and oral manifestations. There is an increase in the activity of the humoral B-lymphocytes of the immune system in conjunction with abnormal function of the T lymphocytes.

Although genetic factors probably play a role in the pathogenesis of SLE, the precise cause is unknown .

### Clinical Features

**Systemic lupus erythematosus:** SLE can be a very difficult disease to diagnose in its early stages because it often appears in a nonspecific, vague fashion, frequently with periods of remission or disease inactivity. Women are affected nearly 8 to 10 times more frequently than men. The average age at diagnosis is 31 years. Common findings include fever, weight loss, arthritis, fatigue , and general malaise. In 40% to 50% of

affected patients, a characteristic rash, having the pattern of a butterfly, develops over the malar area and nose. Sunlight often makes the lesions worse.

The kidneys are affected in approximately 40% to 50% of SLE patients. This complication may ultimately lead to kidney failure; thus it is typically the most significant aspect of the disease.

Cardiac involvement is also common with pericarditis being the most frequent complication.

Oral lesions of SLE develop in 5% to 25% of these patients. The lesions usually affect the palate, buccal mucosa, and gingivae. Sometimes they appear as lichenoid areas, but they may also look non specific or even some what granulomatous. Involvement of the vermilion zone of the lower lip (lupus cheilitis) is sometimes seen. Varying degrees of ulceration, pain, erythema, and hyperkeratosis may be present. Other oral complaints such as xerostomia, candidiasis, periodontal disease, and dysgeusia have been described, but the direct association of these problems with SLE remains to be proven.

## Histopathologic Features

The histopathologic features of the skin and oral lesions of the various forms of lupus erythematosus show some features in common but are different enough to warrant separate discussions. The skin lesions of SLE are characterized by hyperkeratosis, often displaying keratin packed into the openings of hair follicles ("follicular plugging"). In all forms of lupus erythematosus, degeneration of the basal cell layer is frequently observed, and the underlying connective tissue supports patchy to dense aggregates of chronic inflammatory cells. in the deeper connective tissue, the inflammatory infiltrate often surrounds the small blood vessels.

The oral lesions demonstrate hyperkeratosis, alternating atrophy and thickening of the spinous cell layer, degeneration of the basal cell layer, and subepithelial lymphocytic infiltration .

Treatment and Prognosis

Patients with SLE should avoid excessive exposure to sunlight because ultraviolet light may precipitate disease activity. Mild active disease may be effectively managed using non-steroidal anti inflammatory agents combined with antimalarial drugs, such as hydroxychloroquine. For more severe, acute episodes that involve arthritis, pericarditis. thrombocytopenia. or nephritis, systemic corticosteroids are generally indicated.

**Discoid Lupus Erythematosus.** DLE is characteristically seen in middle age, especially in women. Lesions commonly appear solely on the skin, most commonly on the face and scalp. Oral and vermilion lesions are commonly seen, but usually in the company of cutaneous lesions. On the skin, lesions appear as disc-shaped erythematous plaques with hyperpigmented margins. As the lesion expands peripherally, the center heals, and formation of scar and loss of pigment are noted. Involvement of hair follicles results in permanent hair loss (alopecia).

Mucous membrane lesions appear in about 3% to 25% of patients with cutaneous DLE. The buccal mucosa, gingiva, and vermilion are most commonly affected. Lesions may be erythematous or ulcerative with delicate white, keratotic striae radiating from the periphery. The diagnosis of oral lesions may not be evident on the basis of clinical appearance. Progression of DLE to SLE is very unlikely, although the potential does exist.

## Pemphigus Vulgaris

Pemphigus is a group of autoimmune mucocutaneous diseases

characterized by intraepithelial blister formation. It results from a breakdown or loss of intercellular adhesion, thus producing epithelial cell separation known as acantholysis. Widespread superficial ulceration following rupture of the blisters leads to painful debilitation, fluid loss, and electrolyte imbalance. Before the use of corticosteroids, death was not an uncommon outcome for patients with pemphigus vulgaris.

Clinical Features.

Lesions of pemphigus present as painful ulcers preceded by bullae. The first signs of the disease appear in the oral mucosa in approximately 60% of cases. Such lesions may precede the onset of cutaneous lesions by periods of up to 1 year. Bullae rapidly rupture, leaving a red, painful, ulcerated base. Ulcers range in appearance from small aphthous-like lesions to large maplike lesions. Gentle traction on clinically unaffected mucosa may produce stripping of epithelium, a positive Nikolsky's sign. A great deal of discomfort often occurs with confluence and ulceration of smaller vesicles of the soft palate, buccal mucosa, and floor of the mouth.

Histopathology and Immunopathology.

Pemphigus vulgaris appears as intraepithelial clefting with keratinocyte acantholysis Loss of desmosomal attachments and retraction of tonofilaments result in free-floating, or acantholytic, Tzanck cells. Bullae are suprabasal, and the basal layer remains attached to the basement membrane.

Treatment and Prognosis.

The high morbidity and mortality rates previously associated with pemphigus vulgaris have been reduced radically since the introduction of systemic corticosteroids.

Topical Steroids: Topical corticosteroids may be used intraorally as an adjunct to systemic therapy, with a possible concomitant lower dose of systemic corticosteroid.

## Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is a chronic blistering or vesiculobullous disease that affects predominantly oral and ocular mucous membranes .It is also known as cicatricial pemphigoid, benign mucous membrane pemphigoid, ocular pemphigus, childhood pemphigoid, and mucosal pemphigoid; when it affects gingiva exclusively, it is referred to clinically as gingivosis or desquamative gingivitis, although these terms are imprecise and not specific in that desquamative gingival alterations are common to other oral mucosal diseases as well.

Clinical Features

This is a disease of adults and the elderly and tends to affect women more than men. MMP has rarely been reported in children. Other mucosal sites that may be involved include the conjunctiva, nasopharynx, larynx, esophagus, and anogenital region. Oral mucosal lesions typically present as superficial ulcers, sometimes limited to attached gingiva . Bullae are not commonly seen because the blisters are fragile and short lived. Lesions are chronic and persistent and may heal with a scar (cicatrix)—particularly lesions of the eye. Risks include scarring of the canthus (symblepharon), inversion of the eyelashes (entropion), and resultant trauma to the cornea (trichiasis). To prevent corneal damage, many patients with ocular pemphigoid have their eyelashes permanently removed by electrolysis. With laryngeal involvement, voice alterations may result from supraglottic stenosis. Cutaneous lesions are uncommon and usually appear in the head

and neck and extremities.

Gingival lesions often present as bright red patches or confluent ulcers extending to unattached gingival mucosa with mild to moderate discomfort. Concomitant ulcers and erosions may be seen on marginal and attached gingiva. Additionally, lesions may be seen on the buccal mucosa, palate, labial mucosa, and lips. With chronicity, the pain associated with oral MMP typically diminishes in intensity. Intact epithelium, especially adjacent to ulcers, can often be stripped away with ease, leaving denuded submucosa. This is one of several mucocutaneous diseases in which a positive Nikolsky's sign may be elicited. Because of patient discomfort, routine oral hygiene is often compromised. This results in dental plaque accumulation, which in turn superimposes an additional, but nonspecific, inflammatory response.

Histopathology and Immunopathology.

MMP is a subepithelial clefting disorder with no acantholysis. In early stages, few lymphocytes are seen, but over time, the infiltrate becomes more dense and mixed.

Treatment and Prognosis.

Corticosteroids are typically used to control MMP ,Prednisone is used for moderate to severe disease, and topical steroids for mild disease and maintenance. Very high systemic doses occasionally are required to achieve significant results in some cases of recalcitrant gingival MMP. Because side effects of therapy may outweigh benefits, high-potency topical steroids are often used instead (e.g., clobetasol, betamethasone dipropionate, fluocinonide, desoximetasone

## Epidermolysis Bullosa

Etiology and Pathogenesis.

Epidermolysis bullosa is a general term that encompasses one acquired and as many as 20 genetic or hereditary varieties (dystrophic, junctional, simplex) of diseases that basically are characterized by the formation of blisters at sites of minor trauma.

Clinical Features

The feature common to all subtypes of epidermolysis bullosa is bulla formation from minor trauma, usually over areas of stress such as the elbows and the knees. Onset of disease is seen during infancy or early childhood for the hereditary forms, and greater with the inherited recessive forms. Blisters may be widespread and severe and may result in scarring and atrophy. Nails may be dystrophic in some forms of this disease.

Oral lesions are particularly common and severe in the recessive forms of this group of diseases and uncommon in the acquired form. Oral manifestations include bullae that heal with scar formation, a constricted oral orifice resulting from scar contracture, and hypoplastic teeth. These changes are most pronounced in the type known as recessive dystrophic epidermolysis bullosa.

Treatment and Prognosis.

The prognosis is dependent on the subtype of epidermolysis bullosa. Behavior ranges from life threatening in one of the recessive forms, known as junctional epidermolysis bullosa, to debilitating in most other forms. Therapy includes avoidance of trauma, supportive measures, and chemotherapeutic agents (none of which is consistently effective). Corticosteroids, vitamin E, phenytoin, retinoids, dapsone, and immunosuppressive agents all have been suggested as providing some

benefit to patients. More recently, IVIg and the monoclonal biologic agent, infliximab, have been associated with some therapeutic success.