General medicine and surgery for dental practitioners: part 5. Immunological disease and dental practice

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IN BRIEF

- Provides an overview of clinical immunology and how it interfaces with dentistry.
- Highlights signs of possible immunodeficiency.
- Discusses oral conditions that may be seen in patients with inherited or induced immunodeficiency states.

PRACTICE

At some stage in clinical practice all dental practitioners will encounter patients with disorders of the immune system. It is therefore important that dental practitioners are aware of the potential implications for safe practice. This paper summarises some of the more common immunological disorders that may be encountered, together with a basic review of immunological processes from a clinical perspective.

INTRODUCTION

The immune system consists of multiple physical, chemical and cellular components to protect the individual from disease. In certain patients, parts of the immune system are absent (immunodeficiency) or react inappropriately against things such as food and drugs (allergy) or the subject's own tissues (autoimmunity). There is a variety of oral conditions that are related to the activity of the immune system.

The components of the immune system have been classified as innate or adaptive. The innate immune system provides a constant level of protection and is the line of first defence against microorganisms. Specific protection is provided by the adaptive immune system, which has a long-standing immunological memory. It adapts (hence the name) over the lifetime of an individual to infections. The innate and adaptive systems work closely together and provide long-lasting immunity to microorganisms that have been encountered.

CLASSIFICATION OF IMMUNE DEFICIENCY

Patients may highlight symptoms or previous disorders that raise suspicion of possible dysfunction of the immune system. Immunodeficiency occurs when one or more components of the immune system are absent or defective. Primary immunodeficiency is often the result of a single gene disorder and may be inherited or the result of a new mutation. Immunodeficiency that results from an insult, such as an infection (eg HIV), disease (eg lymphoproliferative disease) or medication (eg immunosuppressants) is termed secondary immunodeficiency. A classification of immunodeficiency is given in Table 1. Potential warning signs of immunodeficiency are given in Table 2.

POINTS IN THE HISTORY

Patients with immunodeficiency usually give a history of excess numbers and severity of infections. Despite this, many patients with immunodeficiency are diagnosed after significant delay, which can result in substantial morbidity and increased mortality. Table 2 shows ten warning signs that should raise suspicion of immunodeficiency.[1]

It is clear from the above that practitioners should check for a history of recurrent infections, a family history of problems with the immune system and relevant drugs.

Table 1 A classification of immunodeficiency

Inherited (primary) immunodeficiency
B cells (lack of antibody)
T cell problems
Combined B and T cell problems
Neutrophil defects/disorders
Complement disorders
Acquired (secondary) immunodeficiency
For example infections such as HIV, lymphoproliferative disease, malnutrition, drugs – immunosuppressives

Table 2 Signs or points obtained from the history that should alert a practitioner to the possibility of immunodeficiency[1]

Eight or more new ear infections in 1 year
Two or more serious sinus infections in 1 year
Two or more pneumonias in 1 year
Recurrent, deep skin or organ abscesses
Two or more deep seated infections, for example osteomyelitis, cellulitis
Antibiotics for 2 months without effect
Surgical intervention for chronic infection, for example recurrent incision of boils
Persistent oral candidosis or cutaneous candidosis after age 1 year
Failure to thrive
Family history of immunodeficiency

Patients with immunodeficiency are clearly more prone to recurrent or serious infections that may be particularly difficult to treat. Most infections will be bacterial or fungal,

GENERAL MEDICINE

1. History taking and examination of the clothed patient
2. The drug box, equipment and basic principles of management
3. Management of specific medical emergencies in dental practice
4. Infections and infection control
5. **Immunological disease and dental practice**

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although serious viral infections may also occur in these patients. Infections may occur with rare or unusual organisms or at unusual sites. Patients with immunodeficiency may also present with relatively common infections, for example oral candidiasis, but it is the persistent nature of infection that may be unusual.

Patients with immunodeficiency are also prone to malignancy and autoimmune disease as they have lost regulatory and surveillance cells that normally keep the immune system in check. Dental practitioners should be particularly vigilant for signs of cutaneous cancers, such as basal cell carcinomas and squamous cell carcinomas on sun exposed surfaces, particularly the lips (Fig. 1).[2] There may be clinical signs that suggest more widespread immune dysregulation such as autoimmune disease resulting in patches of skin depigmentation, a condition known as vitiligo, or hyperpigmentation can occur as the result of Addison's disease.

Examples of specific primary immunodeficiencies that may be seen in dental practice include:

- C1 esterase inhibitor deficiency (hereditary angioedema) is a condition that may be inherited resulting in uncontrolled activation of the complement pathway. Significant soft tissue swelling can occur after exposure to minor trauma or stress such as dental treatment (Fig. 2). Laryngeal ooedema is particularly important as it can lead to airway obstruction. One of the means of distinguishing the condition from anaphylaxis is that urticaria does not occur. Treatment of acute attacks is with replacement of the missing enzyme and clearly patients with this condition should be managed in conjunction with an immunologist. Prevention is always best and before dental treatment patients may require supplementation with a C1 esterase inhibitor concentrate
- Chronic mucocutaneous candidosis (CMC) is a rare condition affecting both sexes. It presents with chronic candida infection of the skin and mucous membranes. An associated autoimmune endocrine deficiency may be found. Regular antifungal treatment at high doses may be required over prolonged periods
- Common variable immunodeficiency (CVID) is a form of antibody deficiency disorder of unknown cause. It may be the result of multiple gene defects. Treatment is with life-long antibody replacement therapy
- Chronic granulomatous disease (CGD) usually presents in childhood with recurrent deep seated abscesses, which may be in unusual sites. The underlying immunological defect is a failure of the neutrophil oxidative burst and subsequent killing of organisms
- Wiskott-Aldrich syndrome (WAS) classically affects males and is associated with eczema, recurrent infections and low platelet counts
- DiGeorge syndrome is a genetic disorder with variable features including congenital cardiac defects, cleft palate and abnormal facial features. It is a disorder of T cell function and leads to predisposition to infection
- Severe Combined Immunodeficiency (SCID) is a genetic disorder leading to impaired function of B and T lymphocytes. Patients may present with chronic diarrhoea, recurrent ear infections, candidosis and respiratory infections due to *Pneumocystis jiroveci*. Haemopoietic stem cell transplants (bone marrow transplants) are the mainstay of management in these patients.

Antibiotic prophylaxis should be considered for procedures that have a high risk of leading to postoperative infection and liaison with an immunologist is important.

ALLERGY

Patients may give a history of allergy, for example to Elastoplast® (Fig. 3). Hypersensitivity reactions are immune-mediated antigen-specific reactions that are either inappropriate or excessive and result in harm to the host. They have been classified by Gell and Coombs[3] (Table 3).

The incidence of allergic disease in western societies is increasing and it is hypothesised that reasons for this may be as a result of a decrease in infections that are encountered and a consequence of immunisation regimens. The proposed 'hygiene hypothesis' suggests that the reduced exposure of the immune system to pathogens has led to a switch in the immune system leading to responses that allow the development of allergic conditions. Changes in the environment, for example changes to housing have led to increased exposure to house dust mites, and dietary changes may also have a part to play.

There are many materials that are used in dental practice that may be considered as irritants or potential allergens. A selection of these is listed in Table 4.

Signs and symptoms can be variable in patients who have an adverse reaction to materials or media used in dentistry. They can range from stomatitis, mouth ulceration, lichenoid reactions (Fig. 4), burning or tingling to lip swelling, oral swelling or facial rashes. More systemic symptoms may arise

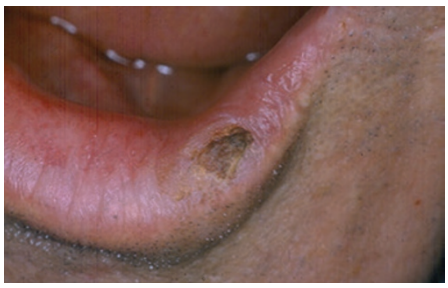

Fig. 1 A squamous cell cancer of the lower lip

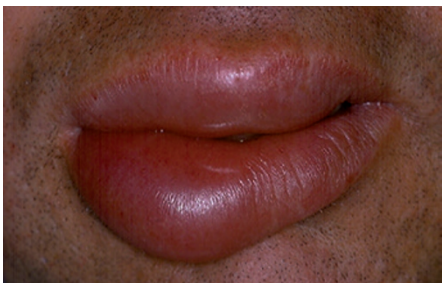

Fig. 2 Lip swelling in a patient with angiooedema

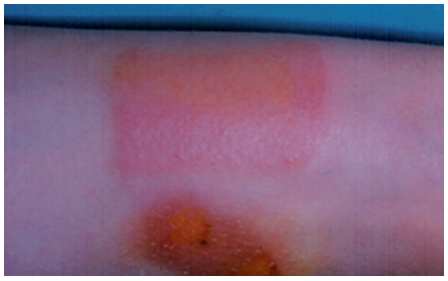

Fig. 3 An allergic reaction to Elastoplast®

Table 3 An abbreviated version of Gell and Coombs' classification of hypersensitivity reactions

Type I	IgE mediated – example allergic rhinitis, asthma, anaphylaxis
Type II	IgG mediated – example transfusion reaction, autoimmune disease
Type III	IgG mediated – example systemic lupus erythematosus
Type IV	T cell mediated – contact dermatitis, chronic asthma, chronic allergic rhinitis

Table 4 Potential irritants/allergens in dental practice

Latex
Mouthwashes
Adhesives
Acrylic
Amalgam
Cements
Impression materials
Antiseptics
Local anaesthetics
Ultra violet radiation

Table 5 Signs and symptoms of an anaphylactic reaction
Itchy rash with or without erythema
Pallor or facial flushing
Upper airway oedema and bronchospasm leading to stridor, wheezing and hoarseness
Vasodilatation leading to hypotension and circulatory collapse
If untreated or rapidly progressive, respiratory arrest and/or cardiac arrest may occur

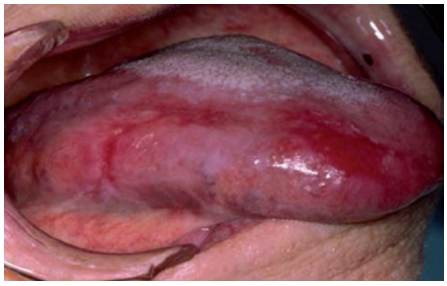

Fig. 4 An intraoral lichenoid reaction

such as urticaria, wheezing or anaphylaxis.

Type I hypersensitivity reactions to chlorhexidine have been seen in patients and healthcare workers,[4] but are not common when the ubiquitous nature of this substance is taken into account. Nevertheless fatal anaphylaxis to chlorhexidine has been attributed to dental use.[4]

ANAPHYLAXIS

Anaphylaxis is a Type I hypersensitivity reaction mediated by IgE to which free antigen binds leading to the release of vasoactive peptides and histamine. The signs and symptoms of anaphylaxis are given in Table 5. The treatment of anaphylaxis is discussed in the paper on medical emergencies in this series.

POTENTIAL FEATURES ON CLINICAL EXAMINATION

Oral lichenoid lesions may cause patients to complain of oral soreness and ulceration can occur. Amalgam has been implicated in the production of oral lichenoid reactions in the tissues that contact restorations with this material.[5] Figure 4 shows a lichenoid reaction. Some patients with this condition have been found to have Type IV sensitivity to mercury and other metals and patch testing may be useful in identifying this problem. Removal of an amalgam restoration adjacent to a lesion may lead to improvement even when patch testing is negative, as these materials can also act as irritants.

Oral erythema can also occur secondary to Type IV hypersensitivity. Implicated substances include acrylic. Cheilitis is an inflammatory eruption of the lip and may be due to contact allergy or irritation from constant licking of lips, atopic dermatitis, infection, usually with *Staphyloccoccus aureus* or iron deficiency.

Candidosis may be seen in immunosuppressed patients. Candidal organisms are highly opportunistic and are present in a dormant yeast phase in a significant proportion of the population. Local and/or systemic factors may lead to the yeast developing to into its pseudohyphal (pathogenic) form. Management of these conditions usually involves eliminating local factors such as poor denture hygiene and antifungal medication. In immunocompromised individuals antifungal treatment may need to be used for a prolonged period. Systemic fluconazole is usually the drug of choice.

Immunosuppressed patients are susceptible to viral infections, in particular those of the herpes group such as herpes simplex and varicella zoster virus.[6] A significant proportion of the population carry these viruses in a latent form having acquired them during childhood. Reactivation occurs if the host is unable to mount a significant immune response to the virus. In immunocompetent individuals these infections are usually self-limiting but in the immunocompromised both infections can be more serious and lead to life-threatening conditions such as herpes encephalitis. Such patients need aggressive management with early antiviral medication.

Other viral infections include the papilloma virus group which leads to lesions anywhere on the skin or oral mucosa. Other virus related lesions may include hairy leukoplakia, which is related to Epstein Barr virus and can be a feature of HIV.

There is a large number of conditions which result from autoimmunity. These conditions can be organ-specific such as hyper or hypo-thyroidism, or non-organ specific, for example rheumatoid arthritis, systemic lupus erythematosus (SLE) and vasculitis.

Certain autoimmune conditions may present with oral signs. Signs of Addison's disease, or autoimmune adrenal insufficiency, include increased pigmentation of skin folds, buccal mucosa and scars. In general terms it can present with symptoms of fatigue and depression.

In Type I diabetes mellitus, where there is immunologically mediated destruction of the islets of Langerhans in the pancreas, oral complications include candida infection, dry mouth, sialosis and glossitis. Severe oral infection can upset glycaemic control and patients are prone to increased superficial infections and poor wound healing.

Patients with coeliac disease may present with aphthous ulceration secondary to anaemia. Some may describe a blistering skin rash known as dermatitis herpetiformis.

Other well-known but relatively rare autoimmune diseases that may be seen by dental practitioners include the vesiculo-bullous disorders pemphigoid and pemphigus. Bullous pemphigoid is seen most commonly in the elderly with subepidermal blisters. Treatment may be with immunosuppression. Pemphigus vulgaris is often associated with non-healing erosions and treatment is with high dose steroids.

Scleroderma is a multi-system disorder characterised by fibrosis of connective tissue. Oral manifestations can include peri-articular involvement of the temporomandibular joint and skin involvement around the mouth leads to microstomia. The tongue may become thickened and stiffened with oral telangiectasia and widening of the periodontal membrane space but without associated tooth mobility. The hands may be affected, which can lead to difficulties with compliance for oral hygiene measures.

Cutaneous manifestations of disorders such as systemic lupus erythematosus (SLE) may include oral ulceration. A photosensitive facial skin rash (classically described as a 'butterfly' rash), alopecia and Raynaud's phenomenon may also be seen.

Clearly one of the best known immunological diseases recognised by dental practitioners is that of Sjögren's syndrome, comprising dry eyes, dry mouth and associated inflammatory arthritis. Clearly the dry mouth may lead to other signs and symptoms from the mouth including impaired taste sensation, gingivitis, difficulty in swallowing, predisposition to candida infection, angular stomatitis and ascending parotitis. The salivary glands may be enlarged.

Behçet's disease, a systemic vasculitis, has significant oral manifestations. Patients with the disease suffer from a clinical triad comprising aphthous type oral ulceration, genital ulcers and iritis. The ulceration can be severe but oral symptoms may occur before the other features. As a result dental practitioners may be the first clinicians to see patients with this disease. There may be associated skin lesions including a folliculitis.

Erythema multiforme is a disorder characterised by recurrent mucosal lesions with or without skin lesions. The typical skin lesion is described as a 'target lesion' due to its characteristic appearance. Many different types of rash can be seen, hence the use of the word multiforme. Severe cases are described as Stevens-Johnson syndrome. Ocular and genital lesions may also be seen.

It is uncertain what causes erythema multiforme but it is thought to be an immune complex disorder with a diverse range of

Table 6 Immunosuppressants which may be encountered by dental practitioners

Drug	Target within the immune system
Ciclosporin and tacrolimus	Inhibits IL-2 production and action. Specific effect on T-helper cells
Corticosteroids	Inhibits cytokine gene expression
Azathioprine	Inhibits purine synthesis
Cyclophosphamide	Binds and crosslinks DNA preventing interfering with DNA replication and transcription (alkylating agent)
Methotrexate	Competitive inhibitor of dihydrofolate reductase. Interferes with thymidine and therefore DNA synthesis
Mycophenylate mofetil	Blocks synthesis of guanine
Monoclonal antibodies	Antibodies of a single specificity. Available to multiple-cytokine and receptor targets

possible antigens ranging from herpes simplex virus (thought to be responsible for most oral manifestations), to mycoplasma and drugs.

On examination, the characteristic clinical appearance is of oedematous, crusted and blood stained lips. Vesicles or bullae may be seen. Treatment is usually via topical corticosteroids, chlorhexidine and possibly in severe cases systemic steroids. If a viral aetiology is implicated or suspected, acyclovir may be prescribed. If the oral signs and symptoms are significantly limiting nutrition or in particular hydration, the patient may need to be admitted to hospital.

DRUGS THAT MAY BE TAKEN BY PATIENTS WITH IMMUNOLOGICAL DISEASE

The largest group of drugs that may be encountered are the immunosuppressants. Clearly patients with other disorders may also take immunosuppressants as well as those with pure immune disease. Some of the more common ones encountered are summarised in Table 6. Most immunosuppressants target the induction phase of the immune system by reducing lymphocyte proliferation.

Immunosuppressants can produce unwanted intraoral effects. Ciclosporin produces gingival hyperplasia and has been reported to cause this side-effect in up to 30% of patients taking this drug.[7] Cyclophosphamide, methotrexate and mycophenylate cause bone marrow suppression, which can lead to oral ulceration[8] as well as a reduced resistance to periodontal disease. As well as increasing the risk of infection, bone marrow suppression can increase postoperative bleeding as a result of thrombocytopenia. A platelet count below 50×10^9/l is a contra-indication to surgery until corrected or a platelet transfusion is administered. Platelet counts of less than 100×10^9/l require the use of local haemostatic measures such as packing with haemostatic gauze and suturing after dental extractions.

Corticosteroids have a dual effect on the periodontium. Their anti-inflammatory effects can offer protection against periodontal breakdown. On the other hand chronic use of steroids may produce osteoporosis, which increases the risk of periodontal disease.[9] Dental practitioners should also remember that methotrexate has an hepatotoxic effect that varies between individuals but may be significant enough to adversely affect liver function, in particular its role in clotting factor metabolism.

Patients on long-term immunosuppressant therapy, such as those who have had organ transplants, are at risk of developing malignancies on the lip[2] as well as other cutaneous cancers. As mentioned above dentists treating these patients should have a high level of suspicion and be vigilant in monitoring the lips, oral mucosa and skin. Any suspicious lesions should be referred for urgent biopsy.

Concurrent therapy with immunosuppressant medication impacts on the drugs the dentist may prescribe. The main groups to note are the non-steroidal anti-inflammatories (NSAIDs) and antibacterials. NSAIDs should be avoided in those taking corticosteroids as this combination can lead to peptic ulceration. Similarly NSAIDs interact with methotrexate leading to an increase in methotrexate toxicity. The toxicity of the latter drug may also be increased by the penicillins. If an alternative antibacterial drug is not feasible then current advice is that patients receiving a penicillin and methotrexate should be carefully monitored during treatment. Monitoring involves measuring platelet levels and blood counts twice weekly for two weeks, with methotrexate levels being taken if the patient becomes symptomatic.[10] NSAIDs also increase the nephrotoxic effects of ciclosporin.

In addition to immunosuppressants patients may be receiving other medications to treat conditions secondary to their underlying disease, for example antimicrobial drugs.

SUMMARY

The study of immunology is a specialist area. There are some fundamental concepts and conditions with which it is essential for a dental practitioner to be familiar for safe clinical practice.

1. Greenwood M, Seymour R A, Meechan J G. *Textbook of human disease in dentistry.* Chapter 4 *Immunological disease.* Wiley Blackwell, 2009.
2. Nolan A, Girdler N M, Seymour R A, Thomason J T The prevalence of dysplasia and malignant lip lesions in transplant patients. *J Oral Med Pathol* 2012; **41:** 113–118.
3. Gell, P G, Coombs R R The classification of allergic reactions underlying disease. *In* Coombs R R, Gell P G (eds) *Clinical aspects of immunology.* Blackwell Science, 1963.
4. Pemberton M N, Gibson J. Chlorhexidine and hypersensitivity reactions in dentistry. *Br Dent J* 2012; **213:** 547–550.
5. McParland H, Warnakulasuriya S. Oral lichenoid contact lesions to mercury and dental amalgam – a review. *J Biomed Biotechnol* 2012; **2012:** 569-589.
6. Westley S, Seymour R, Staines K. Recurrent intra-oral herpes simplex 1 infection. *Dent Update* 2011; **38:** 368–370, 372–4.
7. Seymour R A, Smith D G, Rogers S R. The comparative effects of azathioprine and cyclosporin on some gingival health parameters of renal transplant patients. *J Clin Periodontol* 1987; **14:** 610–613.
8. Weng R R, Foster C E 3rd, Hsieh L L, Patel P R. Oral ulcers associated with mycophenolate mofetil use in a renal transplant recipient. *Am J Health Syst Pharm* 2011; **68:** 585–588.
9. Wactawski-Wende J, Grossi S G, Trevisan M *et al.* The role of osteopenia in oral bone loss and periodontal diseases. *J Periodontal* 1996; **67:** 1076–1084.
10. NHS National Electronic Library for Medicines. *What is the clinical significance of the interaction between methotrexate and penicillins?* NHS National Electronic Library for Medicines, 2013.