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Proliferation of the gingiva: aetiology, risk factors and treatment modalities for gingival enlargement*



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Gingival enlargement can have a variety of causes. In addition to gingival inflammation, a genetic background as well as haematological diseases have been described as aetiological factors. Systemic medication can also lead to gingival enlargement: cyclosporin, calcium channel blockers and phenytoin are particularly linked to this periodontal disease. However, the development and progression of drug-induced gingival enlargement often can often not be explained simply by the medication itself. Other factors play a role in the pathogenesis, the most important risk factors being bacterial plaque and the resulting gingival inflammation. Careful, non-surgical, anti-infective therapy can achieve a marked improvement in many cases and complete resolution of the enlargement in some cases. If periodontal surgical measures are necessary, external gingivectomy of the tissue can be performed conventionally with a scalpel or alternatively by laser. Gingival enlargement can recur even after successful treatment, which is why regular and thorough aftercare of these patients is important.

■ Introduction

The most common cause of gingival enlargement is inflammation of the marginal gingiva. Any gingivitis causes swelling or thickening of the gingiva as a result of increased perfusion of the blood vessels and the exudation of serum. However, severe inflammation-induced enlargement usually only happens if the inflammatory reaction is intensified by local and/or systemic factors. The local factors include tooth displacement, overhanging crown and filling edges as well as fixed orthodontic appliances.

In children and adolescents undergoing orthodontic treatment, however, the gingival inflammatory reaction is not influenced merely by local factors, but also by systemic, endocrine factors. The female sex hormones progesterone and oestrogen, for instance, promote primarily plaque-induced gingivitis as they can be metabolised by certain periodontal pathogens and thereby offer a growth advantage to these microorganisms¹. They additionally increase the permeability of the vessels and reduce the degree of keratinisation of the gingiva, which makes the oral gingival epithelium more permeable and more

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Figs 1a to 1c Different forms of drug-induced gingival enlargement. (a) Gingival enlargement induced by cyclosporin (by kind permission of B. Strauß, Frankfurt am Main). (b) Gingival enlargement induced by calcium channel blocker. (c) Gingival enlargement induced by phenytoin.

susceptible to bacterial antigens². As an endocrinological disease, diabetes mellitus can also promote the gingival inflammatory reaction. If blood sugar levels are not checked and tightly controlled, glycation of proteins and lipids may result, leading to the formation of advanced glycation end-products (AGEs). These AGEs bind to specific receptors (RAGEs), which are expressed on macrophages or gingival fibroblasts, for example, and thereby activate the synthesis of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF- α) and interleukin-1 beta (IL-1 β)³. AGEs may also bind to gingival collagen fibres. As a result, the collagen fibres are cross-linked to form stable molecules, which are broken down less well enzymatically and thus accumulate in the connective tissue⁴. Furthermore, disorders in the chemotaxis, adherence and phagocytosis of polymorphonuclear neutrophilic granulocytes (PMNs) and a reduction in the synthesis of collagen fibres have been described in diabetics³.

Hereditary (idiopathic) gingival enlargement is very heterogeneous both clinically and in terms of its genetic background. The enlargements are most pronounced during the eruption phase and may even prevent proper eruption of the teeth⁵. The gingiva usually displays a solid, compact tissue consistency and is barely subject to inflammatory change. Hereditary gingival enlargement may manifest itself as an isolated disease or as a symptom of various syndromes (including Zimmermann-Laband, Rutherford and Cross syndrome)⁵.

Where gingival enlargement develops quickly

and no clear pathogenesis can be identified, medical investigations should be carried out whenever a haematological disease is suspected. The acute form of leukaemia, in particular, can lead to severe gingival thickening as a result of leukaemic cells being deposited in the gingiva. Other typically oral signs of leukaemia would be necrosis or ulceration of the gingiva and the tendency to spontaneous bleeding⁶.

Many cases of enlargement are due to systemic medication, and three drugs or groups of drugs are specifically linked to gingival enlargement: cyclosporin (CsA), calcium channel blockers and phenytoin (Fig 1)^{7,8}.

■ Risk factors for drug-induced gingival enlargement

The prevalence of drug-induced gingival enlargement varies markedly, depending on the medication taken and also on the group of patients studied^{8,9}. Table 1 summarises the frequencies of drug-induced gingival enlargement given in the literature. While a prevalence of approximately 50% is described for phenytoin, the rate for CsA and calcium channel blockers is only about 5% to 30%. These findings suggest that the occurrence as well as the severity of drug-induced gingival enlargement cannot merely be explained by the medications taken. As with most periodontal diseases, the origin and course of drug-induced gingival enlargement can best be described by a multifactorial model with various risk factors (Fig 2)^{4,8,10}.

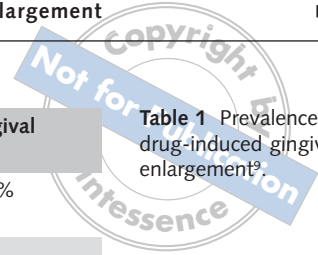


Table 1 Prevalence of drug-induced gingival enlargement⁹.

	Active substance	Product name (examples)	Prevalence of gingival enlargement
Immunosuppressants	Cyclosporin	Sandimmun®, Neoral®	Adults 25% to 30% Children > 70%
Calcium channel blockers	Nifedipine	Adalat®, Aprical®, Corinfar®, Duranifin®	6 to 15 %
	Diltiazem	Dilsal®, Dilta®, Corazet®	5 bis 20 %
	Verapamil	Azupamil®, Cordichin®, Falicard®, Isoptin®, Vera®	< 5 %
	Felodipine	Felobet®, Felocor®, Munobal®	rare
	Amlodipine	Norvasc®	rare
	Isradipine	Lomir®, Vacsal®	not described
Anticonvulsants	Phenytoin	Epanutin®, Phenhydan®	50%
	Carbamazepine	Tegretal®	not described
	Vigabatrin	Sabril®	rare
	Phenobarbital	Luminal®	< 5 %
	Valproate	Convulex®	rare

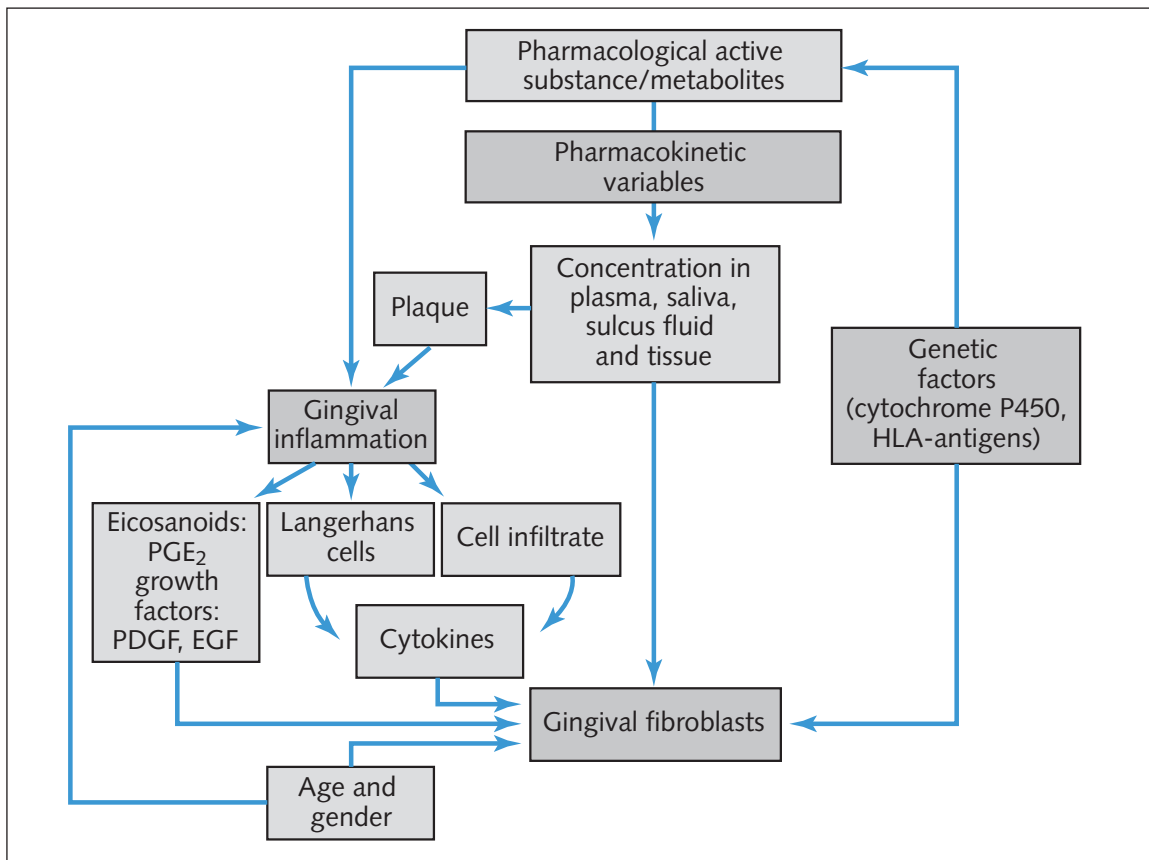


Fig 2 Multifactorial pathogenesis model of drug-induced gingival enlargement¹⁰.

The following risk factors have been identified to date:

- the patient's age and gender;
- taking additional medicinal products;
- pharmacokinetic variables;
- bacterial plaque and the resulting inflammatory state of the periodontal tissue;
- genetic factors^{4,8,10}.

The patient's age is regarded as the most important risk factor for the development of gingival enlargement, especially with reference to taking CsA and phenytoin. The influence of age, which is in inverse correlation to the prevalence of gingival enlargement, indicates a hormonal connection. One possible explanation lies in the interaction between gingival fibroblasts and the androgens circulating in the blood, which are increased in adolescents. Testosterone can be broken down by gingival fibroblasts into dihydrotestosterone. This is an important active metabolite, which has an anabolic action and thus can lead to increased synthesis of connective tissue matrix molecules (e.g. type I collagen)¹¹.

Drug-induced gingival enlargement seems to be up to three times more common in men than women. However, a gender-specific influence cannot be clearly proved for all the drugs.

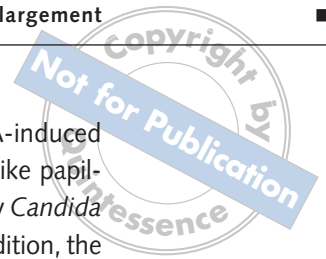
The connection between gingival enlargement and pharmacokinetic variables, such as dosage and concentration of active drug in blood, saliva or sulcus fluid, has been thoroughly investigated and much debated^{7,10}. Despite all the reservations, it is assumed that at least a certain serum concentration of active drug must be exceeded for enlargement of the gingiva to occur. However, this threshold differs between individuals and from drug to drug and is therefore unsuitable as a prognostic factor for gingival enlargement^{7,10}.

It was shown in a longitudinal study that the form of administration of medicines can influence the prevalence and severity of gingival enlargement. Renal transplant patients who took CsA as a suspension dissolved in milk developed enlargement less frequently than the control group taking CsA in capsule form, but the enlargement was far more severe¹². This observation suggests that CsA might accumulate locally in saliva or in bacterial plaque, which is why very much higher concentrations are found locally than for those medicines that can be measured systemically¹³. This theory is also borne out

by the clinical observation that gingival enlargements always start in the interdental space, in other words where the greatest build-up of plaque can be seen. As an aetiological factor of gingival inflammation, plaque plays a further role in the pathogenesis of gingival enlargement.

Any plaque-induced gingivitis leads to increased gingival enlargement^{7,10}. This observation shows that individual oral hygiene is one of the key risk factors for the occurrence and severity of drug-induced gingival enlargement. The evidence of a connection between oral hygiene and gingival enlargement does largely come from cross-sectional studies in which both parameters were tested simultaneously at a specific time point. However, since gingival enlargement promotes the accumulation of large amounts of bacteria owing to the formation of pseudo-pockets, gingivitis can also develop as a secondary condition. In a longitudinal study on the influence of an intensive oral hygiene programme with regular professional tooth cleaning, combined with instructions and motivation to maintain effective individual oral hygiene at home, it was shown that the prevalence and severity of gingival enlargement can be reduced by this regimen but enlargement cannot be prevented in all cases¹⁴. Despite these reservations, there is no doubt that improving individual oral hygiene and reducing gingival inflammation by non-surgical means can have a pronounced effect in terms of preventing and treating this condition. The connection between plaque-induced gingivitis and gingival enlargement is also clear in the currently valid classification of periodontal diseases¹⁵. In this classification, drug-induced gingival enlargement as a subgroup belongs to the category of plaque-induced gingival diseases.

Monotherapy with one of the medicines described here is rarely carried out. In particular, transplant patients treated with CsA additionally take calcium channel blockers because of the CsA side effects and also to improve the bioavailability of CsA. A combination of CsA and calcium channel blockers can increase the prevalence of gingival enlargement but the severity does not appear to be influenced by the combination¹⁰. Combining various anticonvulsant drugs also increases the risk of gingival enlargement because the hepatic degradation of phenytoin to phenylhydantoin is increased. Phenyl-



hydantoin causes gingival enlargement in animal studies¹⁶.

Genetic factors are also under discussion with regard to between-individual differences in the prevalence of gingival enlargement^{7,10}. Gingival fibroblasts of different patients differ in form and size. The difference is not merely confined to the phenotype but also to the ability of the fibroblasts to synthesise proteins. Polymorphisms of enzymes that are involved in the transport (P-glycoprotein MDR1, CYP2C) and metabolism (cytochrome P450) of the pharmacological active substances are among the aspects that have been investigated in studies. A relationship has also been described between gingival enlargement and the expression of human leukocyte antigen (HLA; HLA-DR2-positive patients show a significantly higher incidence of enlargement)¹⁷. T cells can only recognise antigens when they are bound to MHC (major histocompatibility complex) molecules and are presented by antigen-presenting cells. These MHC molecules are identified as HLA antigens and divided into two categories. As patients are routinely tested for HLA antigens before transplantation, this factor may be suitable as a genetic marker to help identify patients at increased risk of gingival enlargement.

■ Clinical and histological changes in drug-induced gingival enlargement

As a rule, gingival enlargement begins to appear one to three months after the start of medication in the region of the interdental papilla and it is usually more pronounced on the vestibular than the oral side¹⁸. The enlargement can be so severe that the papillae appear to be growing together on the oral and vestibular tooth surfaces. The enlargement is generally confined to the keratinised gingiva but it can also extend so far coronally that the patient's speaking and eating are impeded. Owing to the increased tissue mass, pseudo-pockets develop that are not accessible for personal oral hygiene. As a result, the tissue usually displays distinct clinical signs of inflammation.

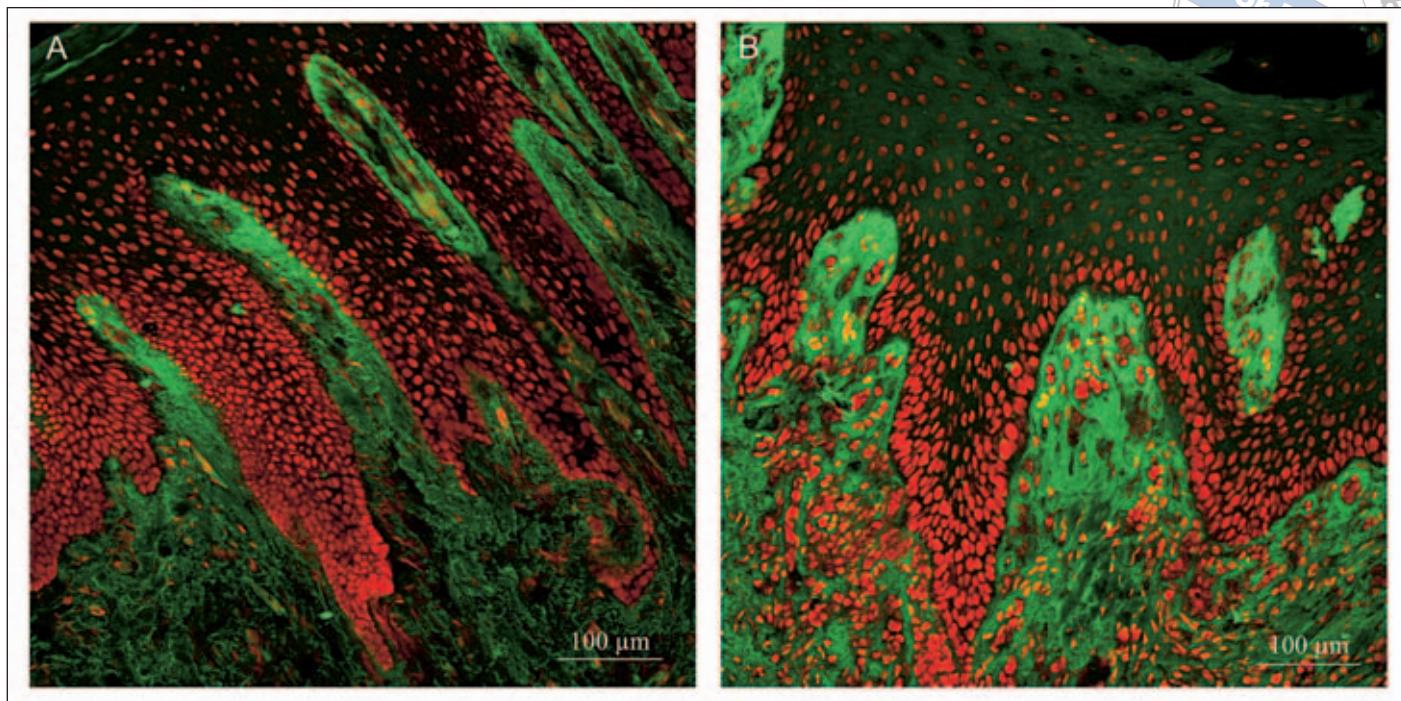
Clinically there are few differences, if any, between most of the forms of drug-induced gingival

enlargement; CsA is the exception. CsA-induced enlargement often displays a cauliflower-like papillary surface, which is presumably caused by *Candida hyphae* penetrating the epithelium¹⁹. In addition, the tissue is generally more perfused and bleeds more easily after mechanical irritation.

Histologically, most gingival enlargements show an increase in subepithelial connective tissue with a varying number of signs of inflammation and, in some cases, thickening of the epithelium⁴. The size of the fibroblasts and their number in relation to the extracellular matrix is not significantly influenced by the pharmacological active substances. This is why the previously common terms 'gingival hyperplasia' and 'gingival hypertrophy' are no longer used.

In healthy individuals, the gingiva is largely made up of connective tissue, over which a multi-layered epithelium lies. The connective tissue is composed of cells (mainly fibroblasts), which are embedded in a matrix of organic molecules. This matrix has several functions. For instance, it acts as a mechanical abutment, helps the alignment and migration of cells and acts as a nutritional store because a lot of growth factors bind to components of the matrix. The extracellular matrix comprises collagen constituents, such as type I and III collagen fibres, but also a large number of non-collagen components, such as proteoglycans, glycosaminoglycans and hyaluronic acid. Under physiological conditions, the matrix components are subject to continuous build-up and breakdown. This balance is controlled by fibroblasts, which synthesise to form a matrix component, such as type I collagen, but also form matrix-degrading enzymes (MMPs, matrix metalloproteinases) or their inhibitors (TIMPs, tissue inhibitors of matrix metalloproteinases). In addition, fibroblasts can also degrade collagen fibres themselves after integrin-mediated phagocytosis.

The balance of matrix components can be disrupted by various stimuli. Whereas plaque-induced gingival inflammation involves increased production of MMPs and hence degradation of connective tissue fibres, drug-induced gingival enlargement may be associated with an accumulation of matrix components, including type I collagen and decorin (Fig 3). The increase in matrix constituents is caused partly by elevated synthesis of fibres but also by disrupted degradation (increased expression of TIMPs)^{20,21}.



Figs 3a and 3b (a) Normal gingiva compared with (b) increased accumulation of type I collagen (green fluorescence) in the subepithelial connective tissue of CsA-induced gingival enlargement; imaging by indirect immunohistochemistry.

■ Treatment modalities

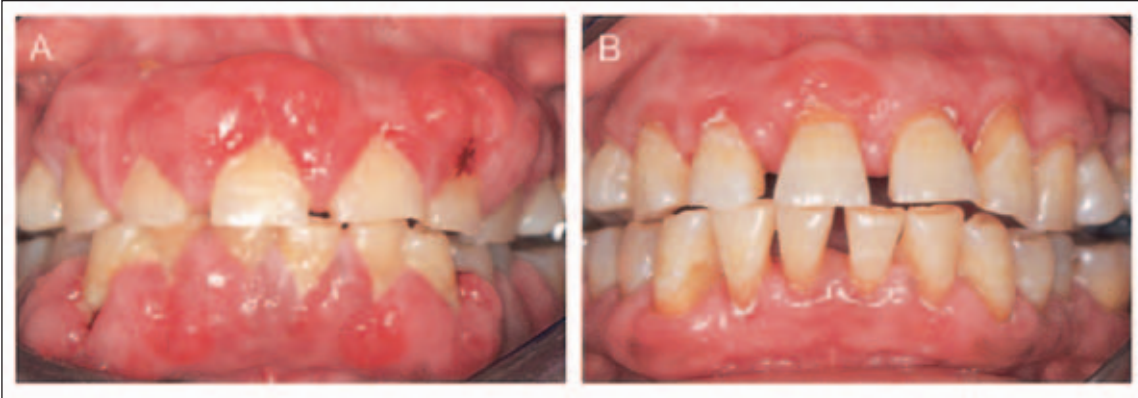
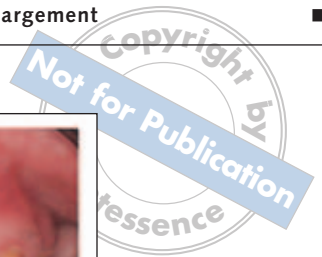
Bacterial plaque and the resulting gingival inflammation are the most important risk factors for drug-induced gingival enlargement that, unlike genetic factors or the patient's age and gender, can be effectively influenced by therapeutic measures. Most treatment options are therefore aimed at reducing bacterial plaque; these include mechanical removal of bacterial deposits in the context of non-surgical treatment, antibacterial mouthwashes, or the systemic administration of antibiotics²². To avoid repeated recurrences, it may be useful to replace the pharmacological active substances responsible in individual cases. If remission of the enlargement is not achieved with non-surgical therapy, however, the overgrown tissue may be removed surgically²².

Before any therapeutic intervention, possible causes of the enlargement of the tissue should be carefully investigated. The case history should include all medications taken, investigation of any modifying factors of a systemic or local nature (mouth breathing, personal oral hygiene habits) and details of how long the enlargement has existed. If a connection with a generalised disease is suspected (e.g. suspected haematological disease), a more

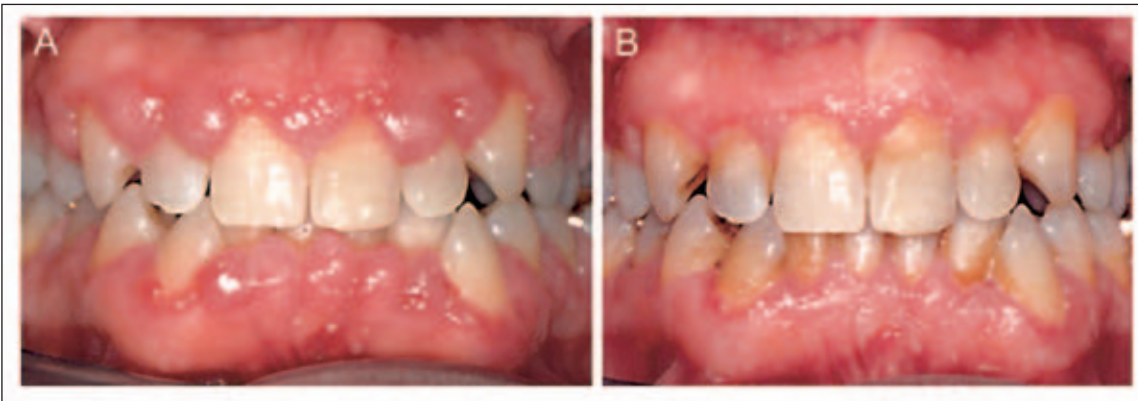
detailed general medical examination must be carried out without undue delay. Thorough documentation of the gingival enlargement (periodontal status, models or photographic records) is valuable to check the patient's progress.

Before dental procedures that might involve a risk of transient bacteraemia, immunosuppressed patients must take antibiotics prophylactically. The drug and the period of medication should always be decided by the attending physician because, especially following liver or kidney transplantation, patients may metabolise certain antibiotics less well, if at all.

A decrease and sometimes complete remission of the enlargement may be observed after non-surgical therapy involving professional tooth cleaning, instructions, and demonstrations to achieve effective individual oral, as well as subgingival, instrumentation of the tooth and root surfaces (Fig 4). Therefore treatment of gingival enlargement should primarily be non-surgical²³. The aim of the therapy, as part of a structured anti-infective treatment, for example with subgingival curettage based on the principle of full-mouth disinfection (FMD)¹⁹, is therefore to remove bacterial deposits as well as supra- and subgingival calculus and thereby reduce the inflamma-



Figs 4a and 4b A 57-year-old patient (a) on calcium channel blocker medication before treatment and (b) three months after anti-infective treatment based on the principle of full mouth disinfection.



Figs 5a and 5b (a) CsA-induced gingival enlargement, and (b) almost complete remission approximately one year after switching the immunosuppressive medication.

tion of the marginal gingiva. In addition, overhanging filling or crown edges, which can encourage the local accumulation of plaque, should be corrected as far as possible.

Using chlorhexidine (CHX) can reduce the prevalence of drug-induced gingival enlargement, but it is also suitable for the non-surgical treatment of drug-induced gingival enlargement, for example as an element of FMD. However, the prolonged use of CHX can have a number of side effects, such as painful erosion of the oral mucosa. Therefore longer-term use of the active ingredient should be reserved for patients at increased risk of recurrent enlargement, as part of a structured aftercare programme.

The systemic administration of antibiotics to treat drug-induced gingival enlargement is also described in the literature²². However, the results of the studies are contradictory and the use of antibiotics does not improve the clinical symptoms in all cases. The effects of metronidazole and azithromycin have been studied in this connection. Metronidazole is a nitroimidazole derivative with a spectrum of action mainly covering

anaerobic microorganisms. However, it also reduces the degradation of CsA, which leads to higher blood levels of the active substance and thereby increases the risk of side effects of CsA. Azithromycin belongs to the group of azalides, which were developed on the basis of macrolides. In principle, the antibacterial mechanism is identical for macrolides and azalides, although azalides display better efficacy against gram-negative bacteria. Another characteristic of azalides is high intracellular accumulation in endogenous defence cells, which results in high concentrations of the active substance particularly in tissues affected by inflammatory changes. In comparison with metronidazole, azithromycin is more effective against drug-induced gingival enlargement, not only because of its antimicrobial action. *In vitro* it increases the phagocytosis of collagen fibres in fibroblasts and thereby counteracts the accumulation of extracellular matrix molecules in connective tissue²⁴.

Nevertheless, the systemic administration of antibiotics to treat drug-induced gingival enlargement should be viewed very critically because of the contradictory study results.



Figs 6a to 6c External gingivectomy in a patient with CsA-induced gingival enlargement. (a) After non-surgical therapy (anti-infective treatment/full mouth disinfection), enlargements still persisted. (b) Enlargements were locally removed by conventional local gingivectomy. (c) Clinical situation two years after the surgical treatment.

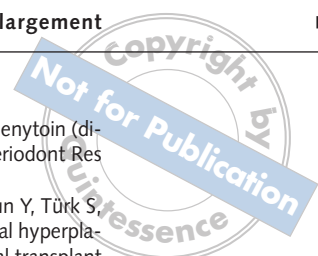
Complete remission of enlargement can be achieved by changing to a different medication (Fig 5). There are now a few alternatives to CsA, e.g. tacrolimus, sirolimus, everolimus, basiliximab and mycophenolate mofetil. In the group of calcium channel blockers, it is possible to change to an alternative active substance with a lower prevalence of gingival enlargement (Table 1) or switch to other antihypertensive drugs (e.g. atenolol, beta-blockers or ACE-inhibitors). Carbamazepine has the same mechanism of action as phenytoin, is also used to treat focally induced epilepsy and is being employed increasingly as an alternative to phenytoin. However, switching to a different medication is complex, particularly for transplant patients and patients on phenytoin therapy, and it does not make sense if the patients tolerate the drugs well and only experience few side effects.

After non-surgical therapy, a clinical re-evaluation of the treatment outcome should be carried out and – if necessary and if the patient agrees – ongoing periodontal surgical measures should be planned in the sense of an internal or external gingivectomy. Good pretreatment of the patient is also important to the long-term success of the surgical therapy because it reduces the inflammatory component and improves wound healing. External gingivectomy is a comparatively quick, safe and easy-to-perform technique but it can also be very radical and associated

with troublesome post-operative problems for the patient (Fig 6). Part of the root surface of the treated teeth often remains exposed after the surgical procedure, so that increased dentine hypersensitivity and aesthetic problems can arise, especially in the anterior region. There is an additional risk of post-operative infection or rebleeding because of the large wound surface that must undergo secondary granulation. However, the risk of rebleeds after external gingivectomy is markedly reduced by careful non-surgical treatment. The risk of rebleeds can also be lessened if the gingivectomy is performed by electro-surgery or by laser^{25,26}. External gingivectomy by laser shows a lower prevalence of recurrence than conventional removal with a scalpel, at least within the first 6 months following the surgical procedure²⁵.

■ Maintenance

Gingival enlargement can recur after anti-infective or surgical therapy. Renewed enlargement may sometimes be observed after only 3 to 6 months²³. The recurrence rate can be markedly reduced by effective personal oral hygiene, supportive professional tooth cleaning and possibly by the patient using a CHX mouthwash. Thorough aftercare of these patients is valuable and essential to prevent recurrent enlargement²².



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