

Nifedipine-induced gingival hyperplasia – pathohistological studies

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Abstract

The pathohistological study of the nifedipine-induced gingival hyperplasia is based on bioptic material from interdental papillae with lobular overgrowth of 3th degree (according to Angelopoulos and Goaz), plaque index = or > 2 (according to Silness and Loe) and gingival index = or > 2 (after Loe and Silness) taken from 8 patients (6 women and 2 men), average age 61 (56-63). All of them had heart and vascular diseases and were treated with nifedipine in the course of at least 9 months, with no data about treatment with other gingival hyperplasia inducing medicaments. The gingival papillae were excised and oriented in a way permitting to investigate the oral or the sulcular part of the hyperplased gingival papilla. Sections were stained with hematoxylin and eosin. The observed parakeratosis with acanthose of the epithelium, forming fine and deep rete pegs, the augmented intercellular spaces, the migration of the immune system cells, the strong vascularisation with dilatation of the vessels and the abundant extravasates are discussed with respect to the nifedipine and the great quantity of bacterial plaque, accompanied by spontaneous bleeding, compared to the healthy gingiva and findings in the experimental human gingivitis.

Key words: gingival hyperplasia, nifedipine, parakeratosis, acanthose, rete pegs, vascularisation, gingivitis, dental plaque.

Introduction

The medicament-dependent gingival hyperplasia was described at the end of 30th (K i m b a l, 1939) and at the early 40th (G l i c k m a n and L e w i t u s, 1941), almost simultaneously in a medical and in a stomatological journal as a side-effect of the hydantoin therapy of epilepsy. After over four decades there appear and increase by number and scope of cases reports on gingival overgrowth after immunosuppressive therapy by cyclosporine A (D j e m i l e v a-K o n o v a, 1990; B u t l e r et al., 1987; P e r n u et al., 1992; R a t e i t s c h a k et al., 1983, Y a n c h e v et al., 1997) as well as after treatment and

prophylaxis with calcium antagonists (all their three prototypes: verapamil, nifedipine and diltiazem) of heart disease, hypertonic disease and rhythmic disorders of the heart activity (D j e m i l e v a, 1993; S l a v c h e v, D j e m i l e v a-K o n o v a, 1993; B a r k l e y et al., 1992; B r o w n et al., 1990; B u t l e r et al., 1987; J o n e s, 1986; L e d e r m a n et al., 1984; N i s h i k a w a et al., 1991; R a m o n et al., 1984; S e y m o u r, 1991; V a n d e r W a l l et al., 1985 etc.). As early as 1989 Djemileva included into the classification of the parodont diseases the medicaments-induced gingival hyperplasia (D j e m i l e v a, 1988; D j e m i l e v a, 1990).

The reports on the induced gingival hyperplasia after a systematic treatment with calcium antagonists (mainly with nifedipine) increase in number all the time, due to the social importance not only of the heart and vascular diseases but of the global parodontal destruction as well. The clinical investigations predominate in the literature. Morphological studies are found in a much lower rate (Barac et al., 1987; Jones, 1986; Lederman et al., 1984; Lucas et al., 1985; Nery et al., 1995; Van der Wall et al., 1985 etc.). In them the presence of parakeratosis with different degree of acantose and deep tubular bendings of the epithelium into the conjunctive tissue are pointed out, the latter forming elongated and often "anastomosing" comb-like forms. Slight changes in the nuclear structure of the epithelial cells are also described. There are, although scarce, data about the increase of fibroblasts, well expressed collagen bundles as well as presence of inflammatory cellular infiltration, particularly in the rich in dilated blood vessels tunica propria. Lately the interests are directed also toward histochemical and immunochemical investigations.

Having in mind the fragmentary data on the pathohistological picture of the nifedipine-induced gingival hyperplasia as well as our own clinical data on the altered morphology of the gingival papillae and the gingival border, which create conditions for a great accumulation of microorganisms in an anaerobic ecological niche with following provocation of inflammatory changes, we undertook the present pathohistological studies.

The aim of the investigation is to describe in a more complete and systematic way the pathohistological findings in nifedipine-induced gingival hyperplasia, expecting that the structural changes of the epithelium, the basal lamina and the lying immediately under it conjunctive tissue will serve us to speculate on the pathogenic mechanisms which determine the influence of the local factors, and the systematic treatment with nifedipine.

Materials and methods

Subject of the study were hyperplastic gingival papillae with lobular overgrowth of 3rd degree after Angeopolous and Goaz (Angeopolous and Goaz, 1972), plaque index = or > 2 after Silness and Loe (Silness and Loe, 1964) and gingival index = or > 2 after Loe and Silness (Loe and Silness, 1963). They belonged to 8 patients (6 women and 2 men) of average age 61 (56 -63) with heart and vascular diseases, treated with nifedipine in the course of at least 9 months and with no data about treatment with other gingival hyperplasia-inducing medicaments. The gingival papillae were excised in the course of a planned gingivectomy under infiltrational anaesthesia with Ultracain S (Hoechst) without vasoconstrictor. Anaesthetic was not introduced intrapapillary in order not to break the structure of the papilla under study. The biopsic tissue was cut into small pieces with a sharp scalpel. They were oriented in such a way as to make possible to investigate the oral and/or the sulcular part of the hyperplastic gingival papilla. The materials were treated following the common histological technics – fixation in 10% formaldehyde solution, embedding in paraffin and a following staining of the sections with hematoxylin and eosin.

Results

The epithelium of the nifedipine-hyperplastic interdental gingival papilla is predominantly parakeratotic, although on the surface of its oral part epithelial cells without nucleus can be found. (In the sulcular part of the gingival papillae surface epithelia with pycnotic nuclei sharply predominate). A strongly expressed acantosis is observed, increasing the thickness of the epithelium by multilining of the suprabasal layer. The epithelium bends considerably into the immediately underlying and deeply situated conjunctive tissue, forming typical "rete pegs", which some-

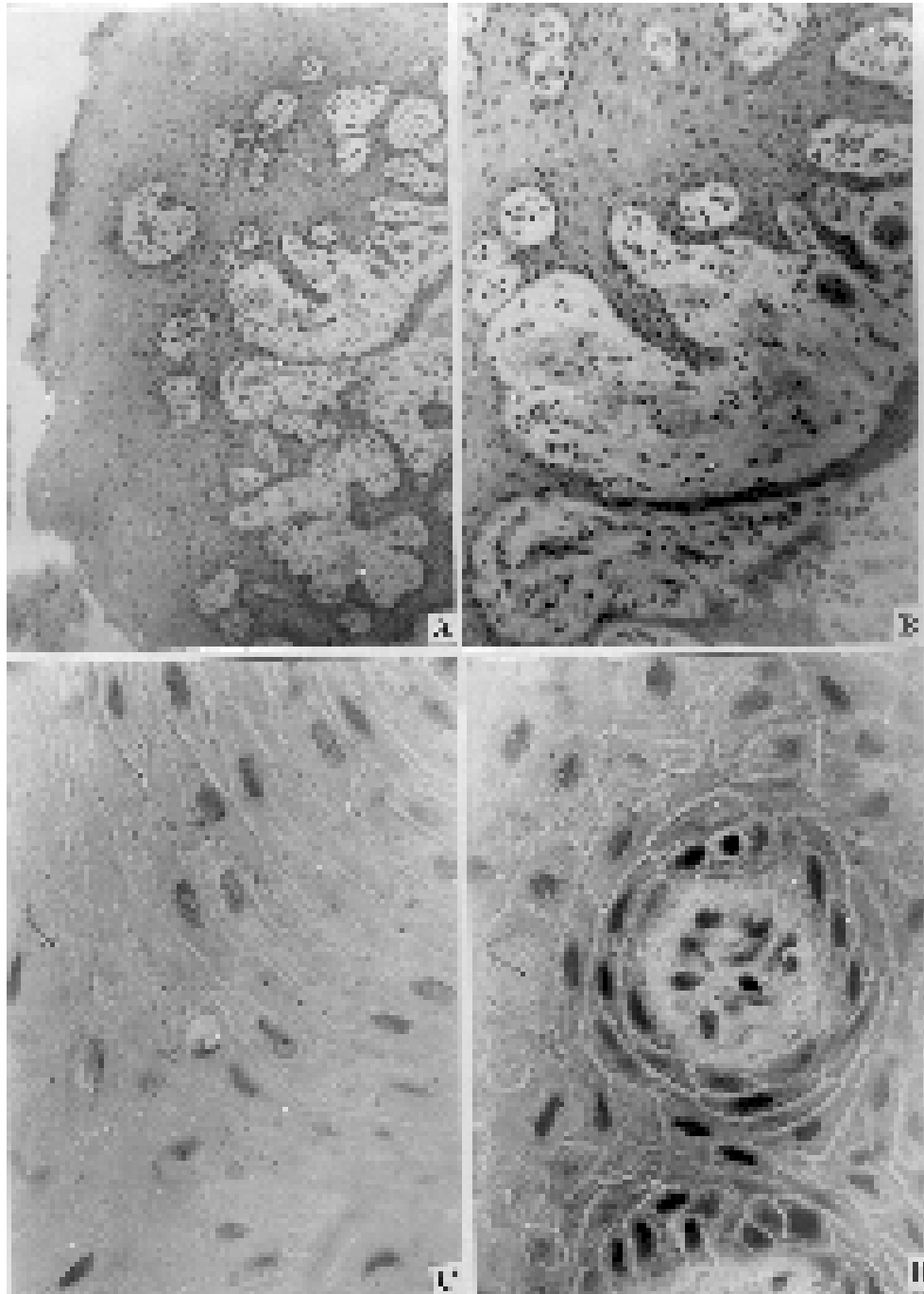


Fig. 1. a) Hyperplasia of the epithelial layer, its “rete pegs” penetrate deep into the lamina propria. Magnification 400x; b) The “rete pegs” are formed by cells of str. germinativum and str. spinosum with elongated nuclei. Magnification 800x; c) The intercellular spaces of the hyperplastic epithelium of str. spinosum are augmented and the cells contact by stretched dismosomes. Magnification 1600x; d) A cell of the immune system in str. germinativum. Magnification 1600x

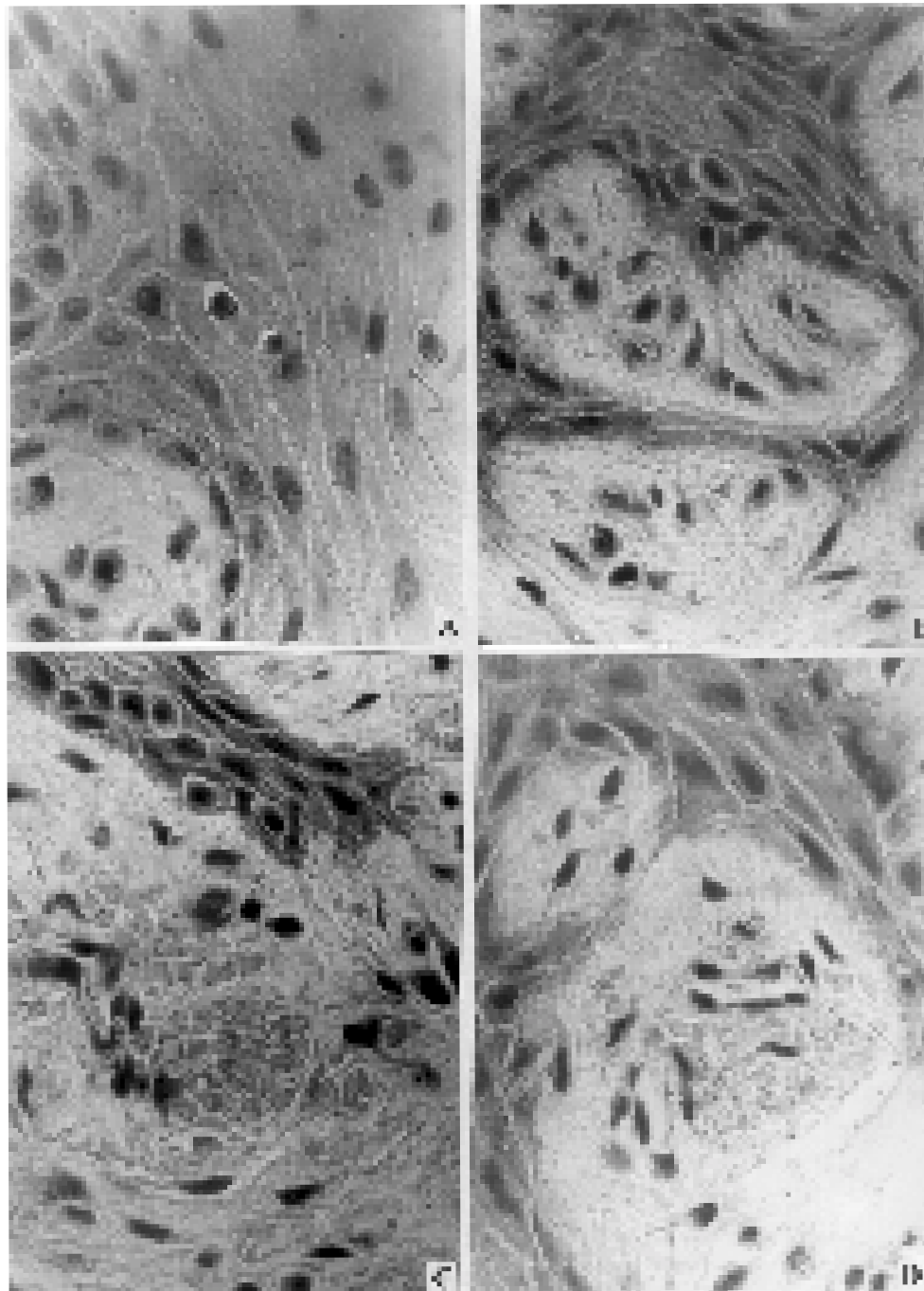


Fig. 2. a and b) Cells of the immune system in str. germinativum and str. spinosum. Magnification 1600x; c) In some places (below) the conjunctive tissue is well presented by fibroblasts and collagen fibres. Magnification 1600x; d) Dilatated blood vessels and thinned walls with a haemorrhage nearby. Magnification 1800x.

times contact each other (fig. 1a). These deep bendings are formed mostly of cells of the germinative and spinose layer, the nuclei of which are more elongated (in parallel with the basal lamina) compared to those of a normal gingival papilla (fig. 1b). The intercellular spaces in the multilayered str. spinosum are augmented and the cells contact each other by stretched desmosomes (fig. 1c). Closely to the basal lamina which is often vaguely outlined migrated cells of the immune system could be found (fig. 1d), which could be observed also in the overlying layers of the epithelium (figs 2a and 2b). The propria in some places is relatively rich in elongated fibroblasts and collagen bundles, but areas of almost unorganized collagen formations are observed as well (fig. 2c). Blood vessels are a frequent find, but their dilatation, the thinning of their walls and even breakage are quite impressive. In many places perivascular extravasates and haemorrhages could be seen (fig. 2d).

The observed pathohistological picture gives the chance to connect some finds to the action of dental plaque microorganisms – the main etiologic factor of the gingival inflammation, and to interpret others as due to the action of nifedipine.

Discussion

Our data from investigations of gingival papillae in experimental and spontaneous catarrhal inflammation in humans (Djemileva-Konova, 1976; Djemileva et al., 1976; Yanchev, Djemileva, 1990) show that the parakeratose layer of the gingival epithelium becomes thinner and not an acantosis but a proliferation of its underlying layers in lateral direction is observed which causes the apparition of the epithelial bendings inwards. They are relatively less deep and wider, with participation not only of the germinative layer. In nifedipine-induced gingival hyperplasia, on the contrary, the epithelium is much thickened and with clearly expressed acantosis and a deep penetration into the conjunctive tissue. It is quite possible

these finds to be caused by the action of nifedipine, especially as they are observed in other medicament and hormone-induced gingival hyperplasiae (according to our unpublished data as well) and are not the result of an independent influence of the dental plaque. The broadening of the intercellular spaces in the deep epithelial layers may be attributed to the action of the microorganisms and their products (enzymes, toxins and allergens), leading to an increased flow of gingival fluid and tissue oedema (Djemileva-Konova, 1976; Djemileva, 1988). Migration of the immune system cells is observed in a healthy gingiva too, caused most probably by the constant contact of the dental plaque microorganisms (and their chemotactic potential!) with the gingiva, but in a very slight degree, within the physiological frames (Djemileva et al., 1976; Yanchev, Djemileva, 1994 etc.). Their presence at a considerably higher frequency in the human experimental gingivitis could be an expression of the gingiva reaction to the bacterial action. In medicament-induced hyperplasia participation of the immune mechanisms may be admitted either as a result of the high plaque index, of the great amount of microorganisms of higher virulence respectively near the gingiva (the ecosystem of the formed deep pseudopockets allows the development of anaerobic microorganisms), or of the still unclear action of the nifedipine. The differentiation of the immune cells must be performed by electron microscopy and immunocytochemical investigations. Besides, the ultrastructural studies would enhance the understanding of the changes both of the epithelial structure and of the basal lamina.

The conjunctive tissue lying immediately under the basal lamina is rich in blood vessels in norm too. In experimental human gingivitis under the action of the dental plaque microorganisms the vascularization increases, but haemorrhages are observed very rarely; so clinically the gingiva bleeding in experimental gingivitis is provoked and not spontaneous (Djemileva-Konova, 1976; Djemileva et

al., 1976; Djemileva-Konova, 1989). On the contrary, the abundant and frequent extravasates close to the dilated vessels (with very thinned and even broken walls!) may be assumed to be a morphological expression of spontaneous bleeding accompanying the nifedipine-induced gingival hyperplasia. Besides, the vessel-dilatating action of the calcium antagonists on the vessels of peripheral type such as the gingival ones must be underlined. This is supported by the communication of a patient about feeling a strong strain in the gingiva half an hour after taking of nifedipine (Djemileva, 1993). We expect to have data on the changes of the fibroblasts and the collagenous fibres after future electron microscopy studies.

Conclusion

The observed pathohistological picture after a study of the nifedipine-induced gingival hyperplasia gives ground to discuss the action of two groups of factors: systemic, raised by the everyday therapy of heart and vascular diseases with nifedipine, and local, connected to the dental plaque and its metabolic products (enzymes, toxins, allergens).

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