Endocrine, *vol. 18, no. 3, 207–210, August 2002* 0969–711X/02/18:207–210/$20.00

Gingival Enlargement in Acromegaly

I. Çapoglu,[1] A. B. Yilmaz,[3] N. Ünüvar,[1] R. Orbak,[5] H. Aksoy,[2] and H. Yesilyurt[4]

Atatürk University Medical Faculty, Departments of [1]Endocrinology, and [2]Biochemistry and Anatomy; and Atatürk University Dentistry Faculty, Departments of [3]Oral Diagnosis, [4]Anatomy, and [5]Periodontology, Erzurum, Turkey

In this study, we investigated gingival enlargement in patients with acromegaly as a component of the disease. Eleven patients (5 males, 6 females) were evaluated. Diagnosis was confirmed with typical clinical features and laboratory. Oral examinations were carried out by the same periodontist. During the examination, plaque index, gingival index, probing pocket depths, and gingival enlargement values were evaluated. Duration of the disease was between 0.2 and 13 yr. Seven patients had pituitary macroadenomas and four had microadenomas during their initial diagnosis. Only one patient was newly diagnosed. The other patients had previously undergone surgery. Gingival enlargement was found in eight patients. Seven patients with gingival enlargement also had prognathism, and one patient had prognathism associated with gingival enlargement. These findings demonstrate that acromegaly that results in overgrowth in various organs should be considered one of the causes of gingival enlargement.

Key Words: Acromegaly; gingival enlargement; organ and tissue changes.

Introduction

Acromegaly is a slow developing disease caused by hypersecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Increased morbidity and mortality associated with the disease make early diagnosis and treatment crucial *(1)*. The prevalence of acromegaly has been estimated to range from 50 to 70 cases per million persons *(2)*. It is an insidious disorder that most commonly occurs between the third and fifth decades *(3)*, and with equal frequency in men and women *(4)*.

The major viscera are enlarged in acromegaly. Skin changes are usually observed in up to 50% of patients *(5)*. Furthermore, some changes appear in the oral cavity; the tongue, soft palate, uvula, and pharyngeal tissues are affected *(6)*.

Received April 23, 2002; Revised June 21, 2002; Accepted June 24, 2002.

Author to whom all correspondence and reprint requests should be addressed: Necdet Ünüvar, Atatürk University PTT, PO Box 56, 25171 Erzurum, Turkey. E-mail: unuvarnecdet@yahoo.com

The etiology of generalized gingival enlargement includes local factors and/or systemic ones such as hormonal changes *(7)* (puberty, contraceptive pills, menstruation, pregnancy, hypothyroidism, and pituitary dysfunction), drugs (phenytoin, sodium valproate, cyclosporine, and nifedipine) *(8–10)*, neoplastic processes *(11)*, and syndromes *(7)*. In approx 50% of cases, gingival enlargement is associated with extraoral conditions *(12)*.

As far as we know, there is no clinical investigation in the literature that explains the relationship between acromegaly and gingival enlargement. We therefore aimed to investigate that association, if any.

Results

Demographic details of the patients are given in Table 1. Of the 11 patients studied, 6 were diagnosed with mild gingival enlargement, 2 with moderate gingival enlargement, and 3 as normal. The mean age of the patients (four females, two males) with mild gingival enlargement was 45.33 ± 7.7 yr, and the duration of the illness was 4.8 ± 3.3 yr. Of the six patients with mild gingival enlargement, only one underwent surgical resection; two underwent surgical resection and octreotide therapy; one underwent surgical resection and radiotherapy; one underwent surgical resection, octreotide treatment, and radiotherapy; and one received no treatment.

Two patients having moderate gingival enlargement were male. The mean age of these patients was 42 ± 19.7 yr, and the duration of illness was 8 ± 7.07 yr. Both cases with moderate gingival enlargement underwent surgical resection and one was additionally treated with octreotide.

The mean age of the patients without gingival enlargement (two males, one female) was 44 ± 2 yr and the duration of illness was 3.6 ± 2 yr. Of the three cases with no gingival disease, two underwent only surgical resection, and one underwent surgical resection, octreotide treatment, and radiotherapy.

Organ and tissue changes in all patients were evaluated. Two of six patients with mild gingival enlargement also had cardiomegaly, three had hepatomegaly, three had goiter, five had skin changes, and four had prognathism (Table 2).

Neither cardiomegaly nor hepatomegaly was observed in three normal gingival patients, but one of them had goiter, two had prognathism, and all had skin changes. Hepatomegaly was found in one of the two patients with moderate

Table 1
Demographic Characteristics of Patients[a]

Patient no.	Age (yr)/sex	AD	Treatment	GI/PI	PPD mean (mm)	GH (μg/L)	IGF-1 (U/mL)	Tumor
1	28/F	3	S + RT	Moderate	6.9	3.8	4.5	Macroadenoma
2	35/M	0.2	—	Mild	3.2	17.4	11.6	Macroadenoma
3	36/M	4	S + RT	Mild	3.6	6.2	4.3	Macroadenoma
4	52/F	8	S + O	Mild	3.0	4.2	3.7	Macroadenoma
5	46/M	6	S + RT + O	None	2.0	1.8	2.1	Microadenoma
6	49/F	7	S + RT + O	Mild	1.8	3.6	1.6	Macroadenoma
7	56/F	13	S + O	Moderate	5.4	6.4	3.3	Macroadenoma
8	51/M	8	S + O	Mild	3.0	4.7	2.8	Macroadenoma
9	44/F	2	S	None	2.1	1.4	1.2	Microadenoma
10	42/F	3	S	None	2.0	1.2	1.3	Microadenoma
11	49/M	2	S	Mild	3.5	1.7	1.5	Microadenoma

[a]AD, acromegaly duration; GI, gingival index; PI, plaque index; PPD, probing pocket depth.

Table 2
Changes in Tissue and Organs

Age (yr)/sex	PI	Cardiomegaly	Hepatomegaly	Goiter	Skin changes	Prognathism
28/F	Moderate	–	–	+	+	+
35/M	Mild	–	–	–	+	–
36/M	Mild	–	–	+	+	+
52/F	Mild	+	+	–	+	+
46/M	None	–	–	+	+	+
49/F	Mild	–	+	+	+	+
56/F	Moderate	+	+	+	+	+
51/M	Mild	+	+	+	+	+
44/F	None	–	–	–	–	–
42/F	None	–	–	–	+	+
49/M	Mild	–	–	–	–	–

gingival enlargement and cardiomegaly in the other, and both had prognathism, goiter, and skin changes.

Discussion

Acromegaly is an uncommon, slowly progressive, and insidious disease, but untreated acromegaly decreases life expectancy *(2)*. The natural history of acromegaly is characterized by chronic progressive disability and a shortened life-span *(13)*.

Skin changes have been described in up to 50% of patients with active acromegaly and are characterized by the presence of new, simple skin tag acrochordons *(5)*. The tongue, soft palate, uvula, and pharyngeal tissues are also affected in acromegaly *(6)*. We are not aware of any clinical investigation that points out the relationship between gingival enlargement and acromegaly. There is only a case report in the literature that presents a patient with acromegaly with hypertricosis and gingival enlargement *(14)*.

Differences between severity and extent of gingival enlargement may be owing to a number of local and systemic factors, such as plaque, hormonal changes, drug ingestion, and heredity influencing gingival overgrowth. Mild and moderate increases in gingival bulk are relatively common, but massive gingival enlargement with associated bone resorption is rare *(15)*.

We aimed to investigate whether there is any relationship between acromegaly and gingival enlargement in patients with acromegaly leading to overgrowth of various organs and tissues. Eleven cases with acromegaly were evaluated and six with mild and two with moderate gingival enlargement were observed. Massive gingival enlargement was not found. While mild enlargement occurred mostly in female patients, two patients with moderate enlargement were male. Two of the three patients without gingival enlargement were male and one was female.

Patients with acromegaly have a gradual progression of symptoms and signs, so the diagnosis is often delayed for

many years. We determined that mild gingival enlargement occurred after 4.8 ± 3.3 yr, and moderate enlargement occurred after 8 ± 7.07 yr from beginning of the disease.

Gingival enlargement was diagnosed as moderate in two and mild in five cases with macroadenoma. On the other hand, while mild gingival enlargement was found in one of four patients with microadenoma. Gingiva was found to be normal in three patients with microadenoma.

Two male patients with moderate gingival enlargement were under age 40. It is known that younger patients tend to have more aggressive tumors, and clinical acromegaly develops relatively rapidly, whereas in older patients the clinical features more often develop insidiously over many years *(13)*.

Macroadenoma was determined in two patients having moderate gingival enlargement, with high GH and IGF-1 levels. Surgical treatment was performed in both patients. In addition, one received radiotherapy and the other octreotide. In five of six patients with mild gingival enlargement, macroadenoma was observed. While GH values were high in five of these patients, IGF-1 levels were normal in three of six patients. The discordance between GH and IGF-1 measurements is an important consideration in the diagnosis of acromegaly and in following up response to treatment *(16)*. Elevated serum GH concentrations are associated with an increased IGF-1 level *(17)*, but the converse is not always true *(18)*.

Gingival enlargement consists of two components: a primary or basic enlargement of connective tissue and epithelium and a secondary complicating inflammatory component. The lesions of gingival enlargement are slow growing and usually painless. Lesions that are relatively firm, resilient, and pink have a greater fibrotic component, with abundance of fibroblasts and collagen fibers *(19)*. Since the action of GH on connective tissue and most of the growth-promoting actions of GH are mediated by IGF-1, there is always a significant correlation between basal propetide of type III procollagen (PIIIP) and plasma IGF-1 levels *(18)*.

Gingival enlargement is a well-described oral side effect of some drug therapies *(20)*. In general, the enlargement develops within a few months of the commencement of drug therapy, is usually generalized *(21)*, and is only partly associated with poor oral hygiene and local plaque accumulation *(22)*. In our study, the relationship between gingival enlargement and duration of illness was established. Although one case was newly diagnosed, the patient had gingival enlargement, implying that gingival enlargement might appear in the early phase of acromegaly.

Our cases were also evaluated for an association between gingival enlargement and organ and tissue changes. Gingival enlargement appeared to be mild in two and moderate in one case of cardiomegaly. The common features of these three cases were that the patients were over age 50 and received octreotide treatment as well as surgery. Symptomatic cardiac disease is observed in 15–20% of patients with acromegaly *(23)*. Furthermore, nodular and diffuse goiter has been reported in 10–40% of patients with acromegaly *(3)*. Goiter was observed in six of our patients. Of these patients, three had mild gingival enlargement, two had moderate, and one was found as normal. The fact that the eastern part of Turkey is an endemic goiter region might be the reason for the high number of goiter cases *(24)*. On the other hand, gingival enlargement was found to be moderate in one, mild in three, and absent in one case with hepatomegaly. Skin changes have been described in up to 50% of patients with active acromegaly *(5)*. In our study, skin changes were observed in eight subjects, and there was gingival enlargement in seven of them.

There was a positive correlation between free marginal gingival thickness and acromegalic disease activity, but there was no correlation between attached gingival thickness and acromegalic diseases.

Our results showed a high prevalence of gingival bleeding in patients. The bleeding was the most apparent feature of gingival inflammation, and a positive correlation appeared between the accumulation of plaque and calculus. In addition, the occurrence of xerostomia owing to radiotherapy, mouth breathing, and anatomic formations that increase plaque accumulation was considered a secondary reason for gingival bleeding. Plaque and calculus deposits, important pathogenic factors of periodontopathy, should be removed either with ultrasound or with hand instruments. If there are gingival pockets, scaling or root planning should be performed to remove calculus. These procedures are basic elements of periodontal treatment and are quite easy, aiming to remove inflammatory tissue and bacterial deposits. Poor oral hygiene as well as insufficient professional dental care contributes to the development of periodontal diseases *(25)*.

In view of the morbidity and, indeed, mortality arising from undiagnosed cases, general dental practitioners and other health care workers should routinely take note of systemic as well as intraoral changes occurring in their patients. The dentist should evaluate and maintain good oral hygiene. Dental visits should be made at least twice a year. However, in the absence of effective oral hygiene, nonsurgical periodontal therapy only retards the progression of destructive periodontitis. It has also been reported that oral hygiene of the patient influences the tissue and may partly mask the response caused by scaling *(26)*.

In conclusion, apart from the other local and systemic factors and usage of certain drugs such as cyclosporine, phenytoin, and calcium channel blocking agents, acromegaly is also responsible for gingival enlargement.

Materials and Methods

Subjects

Eleven patients (five males and six females; age: 44.36 ± 8.45 yr) were studied. Acromegaly was previously diagnosed by their typical clinical features and confirmed by

failure to suppress GH below 2 μg/L after a 100-g oral glucose load.

During the initial diagnosis, seven patients had a pituitary macroadenoma and four patients had microadenoma. Duration of the disease in the patients was changed between 0.2 and 13 yr. One patient was recently diagnosed and had never been treated for acromegaly before. Ten patients underwent surgery, and the tumor could not be completely removed in five of them, so the disease could not be controlled. Therefore, they all received octreotide, a somatostatin analog, while only four were treated with radiotherapy.

The main anthropometric and clinical characteristics of the patients studied are given in Table 1. All periodontal clinical evaluations were performed in the Department of Periodontology by the same periodontist and plaque index (PI-Silness Löe) *(27)*, gingival index (GI-Löe Silness) *(28)*, probing pocket depths, and gingival overgrowth (GH-Pernu) were evaluated *(29)*. Gingival evaluation was classified as normal, mild enlargement, and moderate enlargement according to the plaque index and gingival index. Subjects taking phenytoin, cycylosporine, calcium channel blocking drugs such as nifedipine, diltiazem, verapamil, and amlodipine; pregnant subjects; subjects with leukemia; and subjects with granulomatosis disease were excluded.

Determination of Serum GH Concentrations

Serum GH concentrations were determined by a chemiluminescent immunometric assay (Immulite; Diagnostic Product, Los Angeles, CA). The lower limit of detection was 0.01 ng/mL (0.026 mIU/L). Inter- and intraassay of coefficients of variation (CVs) were 5.8 and 6%, respectively.

IGF-1 Measurement

For IGF-1 measurement, a two-side nonextraction immunoradiometric assay was used (DSL-2800 IGF-1 IRMA). Minimum detection limit was 2.06 ng/mL, and inter- and intraassay CVs were 5 and 4.9%, respectively.

Statistical Analysis

All serum samples were analyzed for GH and IGF-1 within a single assay to avoid interassay variations.

Acknowledgments

We would like to thank S. Melmed for his critical review of and contributions to the manuscript.

References

1. Ben-Shlomo, A. and Melmed, S. (2001). *Endocrinol. Metab. Clin. North Am.* **30,** 565–583.
2. Alexander, L., Appleton, E. M., Hall, R., Ross, W. M., and Wilkinson, R. (1980). *Clin. Endocrinol.* **12,** 71–79.
3. Grisoli, F., Leclercq, T., Jaquet, P., Guibout, M., Winteler, J. P., Hassoun, J., and Vincentelli, F. (1985). *Surg. Neurol.* **23,** 513–519.
4. Thorner, M. O., Vance, M. L., Laws, E. R., Horvath, E., and Kovacs, K. (1998). In: *Williams textbook of endocrinology.* Wilson, J. D., Foster, D. W., Kronenberg, H. M., and Larsen, P. R. (eds.). W.B. Saunders: Philadelphia.
5. Clemmons, D. R., Van Wyk, J. J., Ridgway, E. C., Kliman, B., Kjellberg, R. N., and Underwood, L. E. (1979). *N. Engl. J. Med.* **301,** 1138–1142.
6. Grunstein, R. R., Ho, K. Y., and Sullivan, C. E. (1991). *Ann. Intern. Med.* **115,** 527–532.
7. Brightman, V. J. (1984). In: *Burket's oral medicine.* Lynch, M. A. (ed.). JB Lippincott: Philadelphia.
8. Syrjanen, S. M. and Syrjanen, K. J. (1979). *Proc. Finn. Dent. Soc.* **75,** 95–98.
9. Daley, T. D., Wysocki, G. P., and Day, C. (1986). *Oral Surg. Oral Med. Oral Pathol.* **62,** 417–421.1
10. Lucas, R. M., Howell, L. P., and Wall, B. A. (1985). *J. Periodontol.* **56,** 211–215.
11. Ferguson, M. M., Stephen, K. W., Dagg, J. H., and Hunter, I. P. (1978). *J. Dent.* **6,** 201–206.
12. Witkop, C. J. Jr. (1971). *Birth Defects Orig. Artic. Ser.* **7,** 210–221.
13. Melmed, S. (1990). *N. Engl. J. Med.* **322,** 966–977.
14. Vontobel, F. (1973). *Helv. Paediatr. Acta* **28,** 401–411.
15. Schmidt, B. L., Pogrel, M. A., Perrott, D. H., and Regezi, J. A. (1995). *J. Periodontol.* **66,** 811–816.
16. Barkan, A. L., Beitins, I. Z., and Kelech, R. P. (1988). *J. Clin. Endocrinol. Metab.* **67,** 69–73.
17. Lamberts, S. W., Uitterlinden, P., and Verleun, T. (1987). *J. Clin. Invest.* **17,** 703–710.
18. Verde, G. G., Santi, I., Chiodini, P., Cozzi, R., Dallabonzana, D., Oppizzi, G., and Luizzi, A. (1986). *J. Clin. Endocrinol. Metab.* **63,** 1406–1410.
19. Fermin, A. and Carranza, J. R. (1996). In: *Clinical periodontology.* Fermin, A. and Carranza, J. R. (eds.). W.B. Saunders: Philadelphia.
20. Marshall, R. I. and Bartold, P. M. (1998). *Oral Dis.* **4,** 130–51.
21. Thomason, J. M., Kelly, P. J., and Seymour, R. A. (1996). *J. Clin. Periodontol.* **23,** 367–371.
22. Nishikawa, S., Nagata, T., Morisaki, I., Oka, T., and Ishida, H. (1996). *J. Periodontol.* **67,** 463–471.
23. Nabbaro, J. D. (1987). *Clin. Endocrinol.* **26,** 481–512.
24. Akarsu, E., Akcay, G., Canatan, H., Coskun, U., Capoglu, I., and Unuvar, N. (2000). *J. Clin. Invest.* **23,** 28.
25. Ship, J. A. (1999). *Physiol. Behav.* **66,** 209–215.
26. Lie, T., Hoof, I., and Gjerdet, N. R. (1987). *J. Clin. Periodontol.* **14,** 149–155.
27. Silness, J. and Löe, H. (1964). *Acta Odontol. Scand.* **24,** 121–135.
28. Löe, H. and Silness, J. (1963). *Acta Odontol. Scand.* **21,** 533–551.
29. Pernu, H., Oikarinen, K., Hietanen, J., and Knuuttila, M. (1989). *J. Oral Pathol. Med.* **18,** 422–425.