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Case Report

Oro-Dental Manifestations in Patients with Acromegaly: A Case Report

Reva Bembi[1]*, Esha Garg[2], Neha Vaid[3], Arpit Sikri[4] and Jyotsana Sikri[5]

[1]Senior Lecturer, Department of Oral Medicine and Radiology, JCD Dental College, Sirsa, Haryana, India

[2]Consultant Oral and Maxillofacial Radiologist, India

[3]Senior Lecturer, Department of Oral Pathology, JCD Dental College, Sirsa, Haryana, India

[4]Senior Resident, Department of Prosthodontics, Maulana Azad Institute of Dental Sciences, New Delhi, India

[5]Senior Lecturer, Department of Conservative Dentistry and Endodontics, Santosh Dental College, Santosh Deemed to be University, Ghaziabad, Delhi NCR, India

***Corresponding Author:** Reva Bembi, Senior Lecturer, Department of Oral Medicine and Radiology, JCD Dental College, Sirsa, Haryana, India.

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Abstract

Acromegaly is an acquired disorder related to excessive production of growth hormone and characterized by progressive somatic disfigurement (mainly involving face and extremities) and systemic manifestations. It is a rare condition, with an estimated prevalence of around 60 per million and an annual incidence of 3 - 4 per million. Analyzing mortality determinants, around 60% of acromegalic patients die from cardiovascular disease, 25% from respiratory causes and 15% from neoplasia. It has tendency towards Mandibular overgrowth, tooth separation and jaw malocclusion which makes its diagnosis important even for dentists.

Keywords: *Acromegaly; Dysmorphic Syndrome*

Introduction

Acromegaly (Acrogigantism) is derived from the Greek words "akros" which means extremities and "megas" means big. The disorder was first described by Andrea Verga, an Italian anatomist, in 1864 [1]. In 1886 Pierre Marie, a famous French neurologist working in La Salpetrière Hospital, in Paris, published the first description of the disease and its pathology [2]. He coined the term 'acromegaly' (initially also known as 'Marie's Malady') and linked it to a distinct clinical disease with a characteristic clinical picture. He wrote (in french): 'A condition characterized by hypertrophy of the hands, feet and the face exists which we propose tobe called "acromegaly" which means hypertrophy of the extremities [3]. Other physicians had also given the disease different names including Alibert in 1822 calling it ''Ge´ant scrofuleux'', Verga in 1864 calling it "Prosopo-ectasia" and Lombroso in 1869 calling it "Macrosomia" [1]. Pituitary source of this disorder was first confirmed in 1909 by Harvey Cushing who is considered as the father of the pituitary surgery [4]. Acromegaly may lead to serious complications and early diagnosis can lead to better quality of life. Dentist might be the first person, whom patients might consult, so one should be well versed with the management of such cases. Hereby we are discussing the dento-oral manifestations of a case having broadened hands and feet, macroglossia, enlarged face with prominent supraorbital region, nose, lips and mild prognathism of mandible, radiographs showing Maxillary arch was contained within the Mandibular arch (cross bite/telescopic bite), the Mandibular anteriors were forwardly placed in relation to maxillary anteriors and open bite, thus a diagnosis of acromegaly was given.

Case Report

A 50 year old female patient reported to the department of oral medicine and radiology with a chief complaint of pain in right and left, upper and lower back tooth region since 6 months. History reveals that pain is sharp, intermittent and non-radiating in nature, which

aggravates on chewing food and relieves on taking medication. Medical history revealed that patient is epileptic and hypertensive and is on regular medication for the same since 15 years. Patient reports of blurring of vision, difficulty in vision especially in sunlight, and also reports frequent headache and joint pains. Patient's daughter reported changes in facial features.

General physical examination revealed a well-built stature and hoarsening of voice. Blood pressure was 220/110 mm hg and pulse rate was 80 beats/min, were recorded. The extremities (hands and feet) were broadened, thickened and stubby. Enlargement of tufts of terminal phalanges was present (Figure 1 and 2). Extraoral examination revealed enlarged face, with prominent supraorbital region, nose, lips and mild prognathism of mandible (Figure 3). Intraoral examination showed dental caries w.r.t 11, 16, 36, 46 and root stumps w.r.t. 26. Tenderness on percussion was there w.r.t 16, 36. Maxillary arch was contained within the Mandibular arch (cross bite/telescopic bite) (Figure 4) and large tongue (Macroglossia) with indentations of teeth on lateral borders of tongue was noticed (Figure 5). The Mandibular anteriors were forwardly placed in relation to maxillary anteriors and open bite was noticed. There was enlargement of sinuses. So, a provisional diagnosis of acromegaly was put forth. In the differential diagnosis Marfan syndrome, Primary hypertrophic osteoarthropathy were considered.

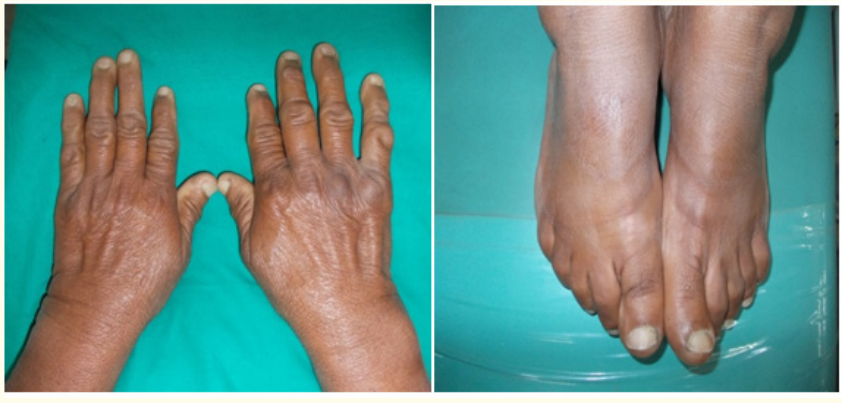

Figure 1 and 2: *Showing enlargement of tufts of terminal phalanges.*

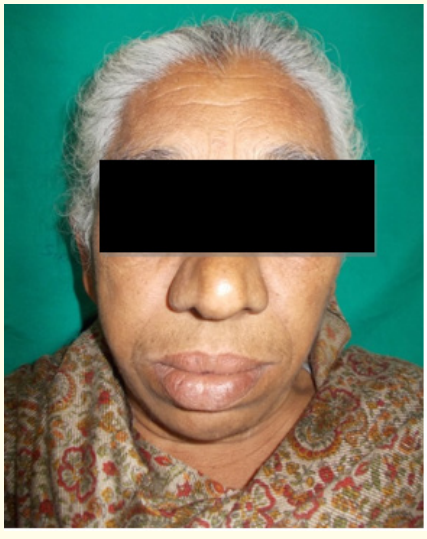

Figure 3: *Showing enlarged face, with prominent supraorbital region, nose, lips and mild prognathism of mandible.*

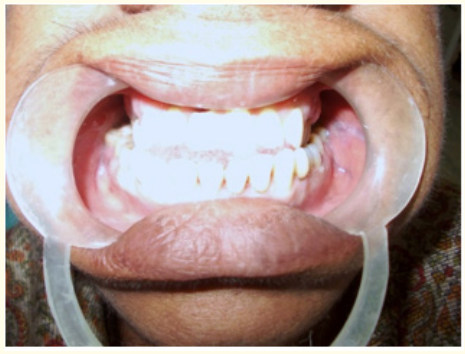

Figure 4: *Maxillary and Mandibular arch showing cross bite/telescopic bite.*

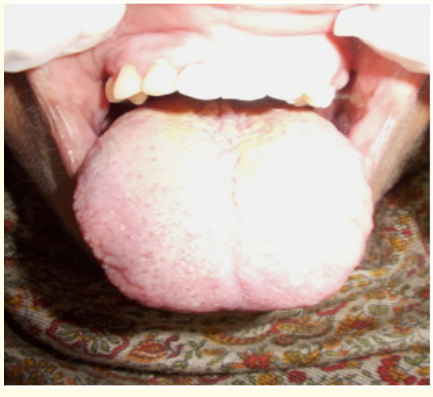

Figure 5: *Large tongue (Macroglossia) with indentations of teeth on lateral borders of tongue.*

Intraoral periapical examination revealed periapical abscess w.r.t 36 and 16, caries w.r.t 46, 11 and root stumps w.r.t 26. Roots appeared to be bulkier suggestive of hypercementosis (Figure 6 and 7). Panoramic radiograph revealed elongated right and left condyles and abnormally increased gonial angle (Figure 8). Lateral cephalogram revealed prognathic mandible, enlarged skull table, enlarged frontal sinuses and steep Mandibular plane (Figure 9). Biochemical findings showed increase in the level of growth hormone (>40 ng/ml) and insulin growth factor (891 ng/ml).

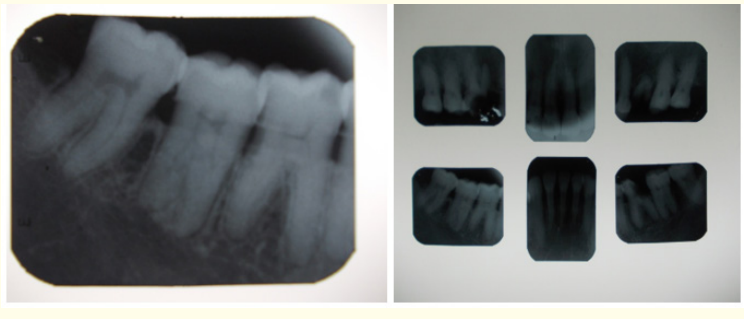

Figure 6 and 7: *Intraoral periapical examination revealed periapical abscess w.r.t 36 and 16, caries w.r.t 46, 11 and root stumps w.r.t 26. Roots appeared to be bulkier suggestive of hypercementosis.*

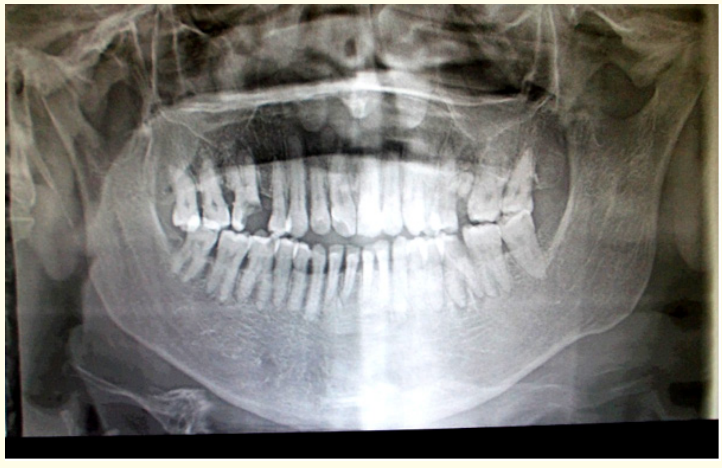

Figure 8: *Panoramic radiograph revealed elongated right and left condyles and abnormally increased gonial angle.*

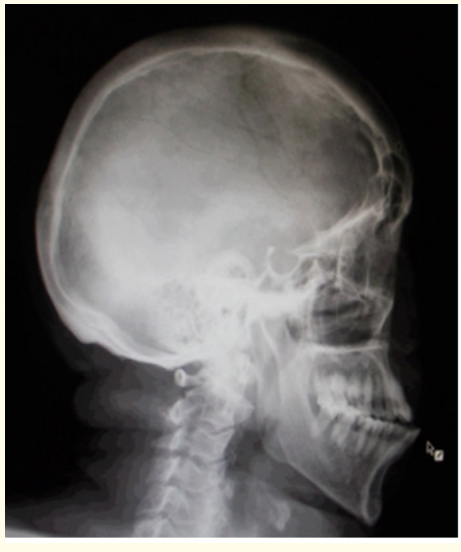

Figure 9: *Lateral cephalogram revealed prognathic mandible, enlarged skull table, enlarged frontal sinuses and steep Mandibular plane.*

In Marfan syndrome, patients have small jaws and have arachnodactyly with positive thumb and wrist signs that distinguish it from acromegaly. In Primary hypertrophic osteoarthropathy, low level of the serum IGF1 which distinguish it from acromegaly.

Thus, based on clinical, radiographic and biochemical findings final diagnosis of Acromegaly was given and the patient was referred to general physician for further evaluation.

The patient was advised endodontic treatment w.r.t 36 and 16, restorations w.r.t 46 and 11 and extraction of root stumps w.r.t 26 followed by prosthetic rehabilitation.

Discussion

Acromegaly is characterized by an acquired progressive somatic disfigurement, mainly involving the face and extremities, but also many other organs, that is associated with systemic manifestations. The disease is related to the excessive production of growth hormone (GH) [5]. Clinical manifestations in each patient depend on the levels of GH and IGF-I, age, tumor size, and the delay in diagnosis. The typical features of acromegaly slowly develop over years; around 40% of acromegalic patients are diagnosed by internists, ophthalmologists if they have visual disturbances, dentists due to maxillary teeth separation, mandibular prognathism, and overbite, gynecologists due to menstrual irregularities and infertility, rheumatologists if they suffer form joint problems, or pulmonologist if they have obstructive sleep apnea [6]. GH is also implicated in other actions that are not mediated by IGF-I, such as anti-insulin, lipolytic and antinatriuretic effects. A recent study found that excess GH in humans is associated with increased activity of the epithelial sodium channel and this could contribute to the volume expansion and soft tissue manifestations seen in acromegaly [7].

The dysmorphic syndrome: The extremities (hands and feet) are broadened, the fingers are widened, thickened and stubby and the soft tissue is thickened as seen in our case. The patient may have had to enlarge his or her ring in recent years, or to change shoe size. The facial aspect is characteristic, and patients with established acromegaly are generally alike in this respect: the nose is widened and thickened, the cheekbones are obvious, the forehead bulges, the lips are thick and the facial lines are marked as seen in our case. The forehead and overlying skin is thickened, sometimes leading to frontal bossing. There is a tendency towards mandibular overgrowth with prognathism, maxillary widening, teeth separation and jaw malocclusion. Photographs show a slow, insidious transformation over several years. The diagnosis is often raised by a doctor who has never seen the patient [8].

Skull radiographs revealed the angle between the ramus and body of the mandible may increase. This, in combination with enlargement of the tongue may result in anterior flaring of the teeth and anterior open bite [9]. The tooth crowns are usually normal in size although the roots of posterior teeth often enlarge as a result of hypercementosis [10]. Same features of open bite, hypercementosis were shown by radiographs of our case

Acromegaly can cause a variety of symptoms, such as malodorous sweating (especially at night); headache (whether the pituitary adenoma is large or small); acroparesthesia (carpal tunnel syndrome); and joint pain. A progressive deepening of the voice [5] same as observed in our patient.

Osteoarticular manifestations: One of the most frequent clinical manifestations of acromegaly affects the joints, in approximately 70% of individuals at the time of diagnosis. Arthralgia is one of the most common complaints of acromegalic patients. Large joint arthropathy is a common feature of the disease, occurring in approximately 70% of patients, resulting from the thickening of cartilaginous and periarticular fibrous tissue, causing joint swelling, pain and hypomobility followed by the narrowing of joint spaces, osteophytosis, and features of osteoarthritis with chronic disease [11]. An early diagnosis of acromegaly is mandatory in order to reduce the severity of spine abnormalities as they are significantly higher in patients with longer disease duration [12].

Cardiovascular manifestations: Cardiac involvement is a consistent feature of acromegaly. Arterial hypertension is considered to be one of the most important prognostic factors for mortality which is present in one third of acromegalic patients [13]. The Blood pressure reported in our case was 220/110 mm Hg so the patient was hypertensive.

GH excess leads to insulin resistance at the level of the liver or in the periphery that leads to hyperinsulinemia, as shown in our case. The prevalence of diabetes in acromegalic patients ranges from 20% to 56%, and that of glucose intolerance ranges from 16% to 46%, depending on the series [5]. There is a link between glucose tolerance, hypertension and acromegalic cardiomyopathy [14].

Respiratory complications: Sleep apnea affects 60% - 80% of all patients with acromegaly (more often men) and 93% of patients with signs of this disorder. Sleep apnea is more likely to be sought in patients who snore (reported by 78% of patients with acromegaly) and those with day time sleepiness (51%), or morning fatigue and morning headache (16%) [15].

Endocrinological manifestations: Hyperprolactinemia with or without galactorrhea develops in approximately 30% of patients due to pituitary stalk compression or mixed tumor secretion of GH and PRL. Hypopituitarism, by mass compression of the normal pituitary tissue, occurs in approximately 40% patients; amenorrhea, impotence, or secondary thyroid or adrenal failure may develop [13].

Gastrointestinal manifestations: The gastrointestinal manifestations associated with acromegaly are colon carcinoma, adenomatous polyps, and dolichocolon [15].

The cancers most frequently studied in acromegaly are colon, breast, and prostate carcinomas, although many others have been described including hematological, bronchial, gastric, esophageal, thyroid, osteosarcoma, pancreas, melanoma, ovarian, renal, adrenal, biliary, carcinoid, cervix, bladder, parotid, astrocytoma, and small intestine cancer [13].

Etiology of acromegaly of pituitary origin

More than 95% of patients with acromegaly have a benign monoclonal pituitary adenoma which develops from the somatotrope cells that normally produce GH in the pituitary. Thus, these adenomas are termed somatotrope adenoma [5].

The pituitary/hypothalamic origin of these adenomas is controversial. Some lines of evidence point to a hypothalamic origin. In this case, the main actor would be growth-hormone-releasing hormone (GHRH), which can cause not only hyperplasia of somatotrope cells but also, as demonstrated in some animal models, actual adenomas [5]. In contrast, the monoclonal nature of the tumors and the absence of relapse after total tumor resection points instead to a pituitary origin. In fact, the initiation and/or progression of malignant transformation of normal somatotropes could be due to a polyclonal hyperplastic response of these cells secondary to hypothalamic dysregulation. The prerequisite for an abnormal response to pathological GHRH secretion may be the existence of a mutation in the somatotrope cell [5].

Genetic syndromes with acromegaly: McCune-Albright syndrome, which is associated with multiple fibrous bone dysplasia, precocious puberty and café-au-lait spots, can be accompanied by acromegaly [16].

Acromegaly can also be associated with hyperparathyroidism, neuroendocrine tumors (e.g. gastrinoma, insulinoma or a non-functional pancreatic tumor), adrenal and other endocrine and non-endocrine tumors in patients with multiple endocrine neoplasia type 1 (MEN1) [17].

When acromegaly is associated with bilateral pigmented micronodular adrenal hyperplasia (causing ACTH-independent hypercorticism) and with cutaneous lesions or cardiac myxomas, the patient should be screened for the Carney complex, which is often related to a Germline mutation of the regulatory 1-α subunit of protein kinase A (PRKAR1A) [18].

Very recently, familial acromegaly related to Germline mutations of the AIP (aryl hydrocarbon receptor interacting protein) gene have been described. These mutations may also, albeit rarely, be responsible for sporadic cases of acromegaly, in particular in young patients [19].

Extrapituitary acromegaly: GH hypersecretion does not always have a pituitary origin. Acromegaly can be due to eutopic hypothalamic GHRH hypersecretion (gangliocytoma, hamartoma, choristoma, glioma, etc.) or, more often, to ectopic, peripheral GHRH hypersecretion (pancreatic or bronchial carcinoid tumor) that stimulate the normal somatotropes to become hyperplastic and to hypersecrete GH. The diagnosis is based on plasma GHRH assay (revealing excess secretion) and on identification of the GHRH-secreting endocrine tumor [5].

GH can also be hypersecreted by an ectopic pituitary adenoma (sphenoidal sinus, petrous temporal bone, nasopharyngeal cavity) or, in exceptional cases, by a peripheral tumor (pancreatic islet tumor or lymphoma) [20].

Diagnosis: Acromegaly is an insidious disease, which is often diagnosed late (between 4 and more than 10 years after onset) [13].

Normal GH production from the pituitary gland is pulsatile; most GH values fall in the range of 0.1 - 0.2 µg/L in normal subjects, with the maximum production occurring at night in harmony with sleep stages. However, there are six to ten secretory bursts during the day, when GH reaches values of 5 - 30 µg/L, which may overlap with the values seen in acromegalic patients [13].

The clinical diagnosis is confirmed biochemically by an increased serum GH concentration as shown in our case and by detection of increased levels of insulin-like growth factor-I (IGF-I) that was also raised in our present case.

Management

According to the 2010 consensus criteria, biochemical control of acromegaly is achieved when circulating IGF-I is reduced to an age and sex-adjusted normal range and GH during OGTT is < 0.4 µg/L or random GH is < 1 µg/L [13].

Therapeutic interventions include surgery, radiotherapy, and medical therapy. Radiotherapy is efficacious in controlling tumour growth and growth hormone secretion; however, achievement of biochemical targets may take up to a decade and a number of safety issues have been raised with this treatment modality [21].

More recently, medical therapy has been increasingly used as primary treatment in selected patients unsuitable for surgery. Clinically available medical therapies for management of acromegaly include dopaminergic agonists, somatostatin analogues, and growth hormone receptor antagonists. Surgical therapy includes transsphenoidal approach and transnasal endoscopic approach frontotemporal craniotomy [22].

Successful management of pituitary adenomas may result in reversal of soft tissue abnormalities. However, bony changes may persist and require corrective orthognathic surgery. Orthodontic and maxillofacial surgeons dealing with corrective orthognathic surgery should be well aware of the complications of this disease. Acromegalic patients may report to the dentist with the complaints of malocclusion, difficulty in speech due to enlarged tongue, mobility of teeth or missing teeth secondary to diabetes mellitus. But prosthetic treatment of the patient with acromegaly often requires close cooperation between the various medical and dental specialties. Unusual problems can be expected because of the large mandible, relatively small maxilla, hypertrophic tongue and increased vertical dimension. Post-insertion care of such a patient requires additional time and effort to enhance the acceptance of the new dentures [23].

Dental management may be complicated by blindness, diabetes mellitus, hypertension, cardiomyopathic dysarrhythmias or hypopituitarism. Thus, invasive or surgical procedures should be carried out only after proper medical evaluation [23].

Conclusion

Acromegaly is an uncommon disease, which in most cases is due to a pituitary tumor. It has a wide variety of clinical manifestations, including acral and soft tissue overgrowth, joint pain, diabetes mellitus, hypertension, and heart and respiratory failure. Acromegaly is usually diagnosed by increased IGF-I and GH. Timely diagnosis by dentists, as dentists can easily identify orodental manifestations that reduces complications and mortality.

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Volume 19 Issue 4 April 2020