

Phenotype and Surgical Treatment in a Case of Proteus Syndrome With Craniofacial and Oral Findings

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Abstract. *Background/Aim: Proteus syndrome is a sporadic disease that is particularly noticeable due to the disproportional growth of body segments. The disease is a genetic mosaic. The mutations can arise from any of the germ layers, an explanation of the very variable phenotype. The aim of this report is to communicate the diagnosis and management of an unusual case of Proteus Syndrome with special attention to oral and craniofacial findings. Case Report: A 15-year-old patient was referred for surgical treatment of pronounced skull malformations and correction of oral mucosal hyperplasia. Treatment caused significant improvement in facial appearance and oral soft tissue conditions. Conclusion: Surgical measures adapted to the local findings and symptoms can often relieve severe disfigurement of the patient.*

Proteus syndrome is a very rare disease which causes a plethora of differentiation disorders and predisposes to certain neoplasms due to early somatic mutations during ontogenesis (1-3). A standardization of findings and symptoms characterizing the entity has been difficult to achieve (4-10) (Tables I and II). The eponymous designation of the disease refers to the diversity of the phenotype (4). In Greek mythology, the sea god Proteus appears on earth and transforms himself into numerous shapes, predominantly to escape captivity. Referring to his capacity of metamorphosis, the medical term 'Proteus' syndrome gives the appealing nominal metaphor for the

characteristic and diverse deformations experienced by affected individuals.

The excessive growth is particularly noticeable when the skeleton is affected. Differences in length and circumference of extremities are just as characteristic of the syndrome as excessive growth of one or more skull bones. The skull is frequently affected by asymmetrical local growth (11). The osseous overgrowth can cause considerable aesthetic and functional impairments (12-15). The report describes diagnostics and treatment of a patient with Proteus syndrome with special consideration of the craniofacial and oral regions.

Case Report

Medical history and physical findings. The 15-year-old female patient was referred to the outpatient clinic of the Department of Oral and Craniomaxillofacial Surgery for treatment of known Proteus syndrome with pronounced craniofacial deformities. It was a sporadic case of disproportionate growth disorders. On admission, the patient was slim (80 kg body weight) concerning her unusually tall height (196 cm). The patient's medical history disclosed an insulin-dependent type I diabetes mellitus, which had been diagnosed several months before, and hypothyreosis following Hashimoto thyroiditis, known for several years.

There was a difference in size between the halves of the body in favor of the left side. The patient had an inclined pelvis resulting of asymmetrical growth in the lower extremities. Orthopedic interventions had already been carried out to compensate the leg length difference and reduce the asymmetry of lower extremities' bones, including wedge excision of growth plates.

The patient's skull was unusually large in general, presented as dolichocephaly and was asymmetrically shaped due to localized osseous growth excess. There was a distinct skeletal plus in favor of the calvarial right side. However, the osseous mass of the forehead was almost centrally located and considerably protruding. In contrast, the glabella appeared flat and the transition to the bridge of the nose was broad and somewhat trough-shaped. The hypoplasia of nasal

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Key Words: Proteus syndrome, osteotomy, gingival hyperplasia, overgrowth syndrome, swallowing dysfunction, spine deformity, cerebriform connective tissue nevus.

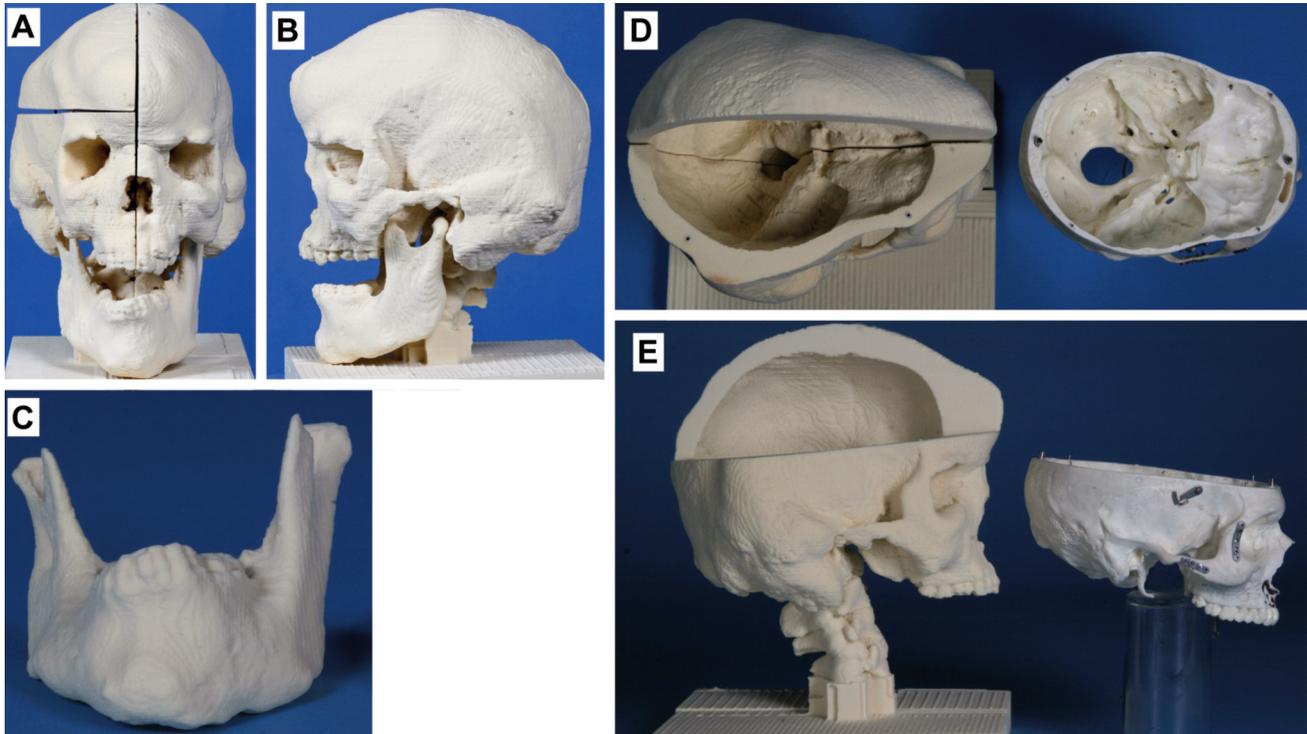


Figure 1. Three-dimensional plastic model of the patient's skull derived from computed tomograms. An artificial model of the skull is shown in Figures 1D and 1E for size comparison. (A) Anterior view with asymmetrically developed calvaria, prominent frontal (bossing) hyperostosis. The supraorbital margins are enlarged. (B) The frontal hyperostosis essentially determines the expression of the profile. Besides frontal hyperostosis, the lateral view of the skull shows excessive growth of the parietal, temporal, and occipital bone. In contrast, the nasomaxillary complex appears underdeveloped around the aperture. The mandible is shown in Figures A and B to illustrate the proportions and in a non-articulating position. (C) Anterior view of the mandible. The asymmetry of the rami is obvious. The mandibular corpus is greatly enlarged on both sides, especially in the cranio-caudal direction. (D) Top view of the skull base after lifting the right side of the skullcap. The calvaria is unevenly thickened. The dolichocephalus is particularly visible in this view. The foramen occipitale magnum is narrowed, which is noticeable in comparison to the exposed skull base of the skull model (right side). (E) The figure shows the thickened calvaria and the enlarged cervical vertebrae with pronounced lordosis. Artificial skull model positioned to the right of the patient model for size comparison.

bones and medial orbital processes of the maxilla, which was only apparent, was caused by the bulging tumor mass of the forehead. However, the maxilla around the apertura piriformis appeared underdeveloped in sagittal projection. The patient had downslanting palpebral fissures and minor ptosis. The orbital cavity was of normal size. Figure 1 shows different aspects of the patient's skull on her three-dimensional skull model.

Both the upper and the lower jaw were developed asymmetrically. Both jaws were considerably enlarged in transverse and cranio-caudal dimension. The vertical enlargement of the viscerocranium contributed significantly to the aspect of the long face. The difference in the vertical dimension of the rami is obvious. The distance between the mandibular canal and the apices of the dental roots was considerable. The asymmetry of the lower jaw also affected the size and shape of the mandibular foramina. There was a discrepancy of mandibular canal diameter in favor of the left side.

The mouth opening was unrestricted at the time of first investigation and this finding did not change during the follow-up of craniomaxillofacial surgical treatment. Mouth was open at rest. Oral inspection revealed generalized hyperplastic oral mucosa and prominent alveolar processes. The patient reported the overgrowth of the oral mucous membranes was first noticed when she was about 10 years old and this finding had increased slowly since then. The tongue was developed symmetrically being of normal size and function. The palate was high arched. The epithelium was of physiological transparency and not inflammatory; leukoplakia was not observed. The oral soft tissue hyperplasia was apparently caused by the mucosal connective tissue. The plus in connective soft tissue caused partial coverage of several tooth crowns by the gingiva and impaired tooth cleaning. The size and shape of teeth was in the normal range. No enamel dysplasia was observed. The dentition showed crowding of anterior and some premolar teeth and compromised occlusion.

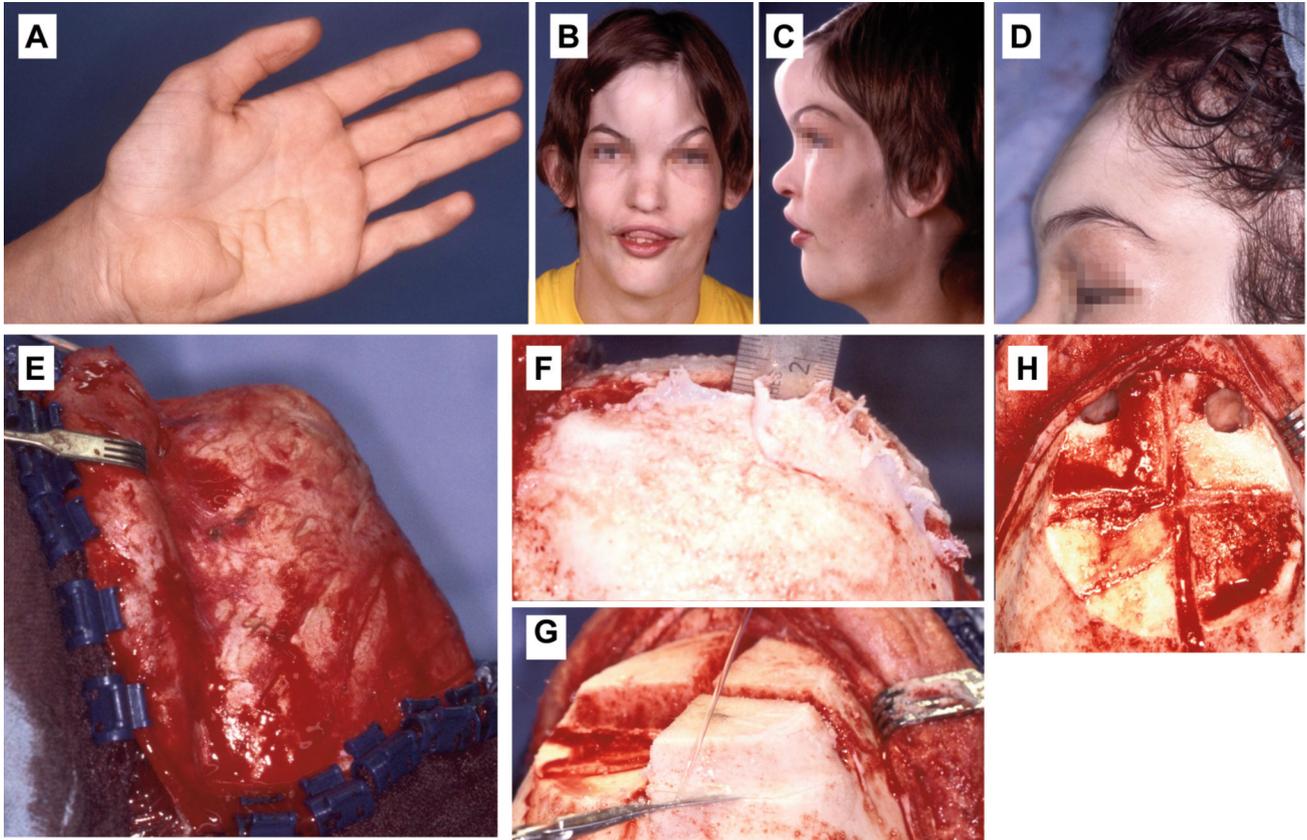


Figure 2. Clinical findings in the patient with Proteus syndrome. (A) Cerebriform cutaneous tissue nevus of left palmar region. Photographs (B) en face and (C) profile of the patient showing a large face with prominent frontal bone, slightly downslanting eye lids, mild ptosis, and mouth open at rest with prominent upper jaw mucosa. (D) The frontal bone appears of normal shape after debulking procedure. (E) Aspect of the frontal bone prior to ablative surgery. (F) The figure shows the diameter of the bone to be ablated. (G) Photograph of segmental frontal bone resection. (H) After osteotomy, the frontal sinuses are temporarily exposed.

On the left palm was noted an unusual and irregular increase of connective tissue. The soft tissue hyperplasia caused some unusual wrinkling of the skin. This finding resembled the characteristic cerebriform skin surface increase known in Proteus syndrome. The fingers were regularly differentiated and functional. Figures 2 and 3 show some physical findings of the patient.

We noted no characteristic nevi of the integument. The integumental findings were recorded on whole body photographs (not shown).

Computed tomography. A computed tomogram (CT) was performed to manufacture a three-dimensional skull model (Figure 1). Axial sectional skull images revealed massive hyperostosis, particularly of the frontal and occipital bones. On the right side there were soft tissue-equivalent opacities in mastoid cells indicating mastoiditis. Individual ethmoidal cells showed masses equivalent to soft tissues and were assessed as swelling of mucous membranes. Both

external auditory canals were subtotally obstructed due to osseous overgrowth.

The cervical spine showed significant changes, which were interpreted as a further syndrome manifestation. Pronounced vertebral hyperplasia was displayed in the range from the foramen magnum down to vertebrae C IV and C V, very pronounced in the arch roots. A noticeable left-sided hypertrophy of the uncovertebral joint was diagnosed in segment C III/C IV. This deformity resulted in stenosing the C IV root on the same side. There was also a central spinal stenosis at this level. However, the patient experienced no sensorimotor deficits in related organs. Figure 4 shows some skeletal findings of the patient.

Ultrasound. Normal-sized thyroid lobes were shown in B-scan ultrasonography of the neck, whereby internal signals of the organ were noticeably low. This ultrasound finding is characteristic of autoimmune hypothyroidism (permanent substitution with L-thyroxine 175 µg/d).

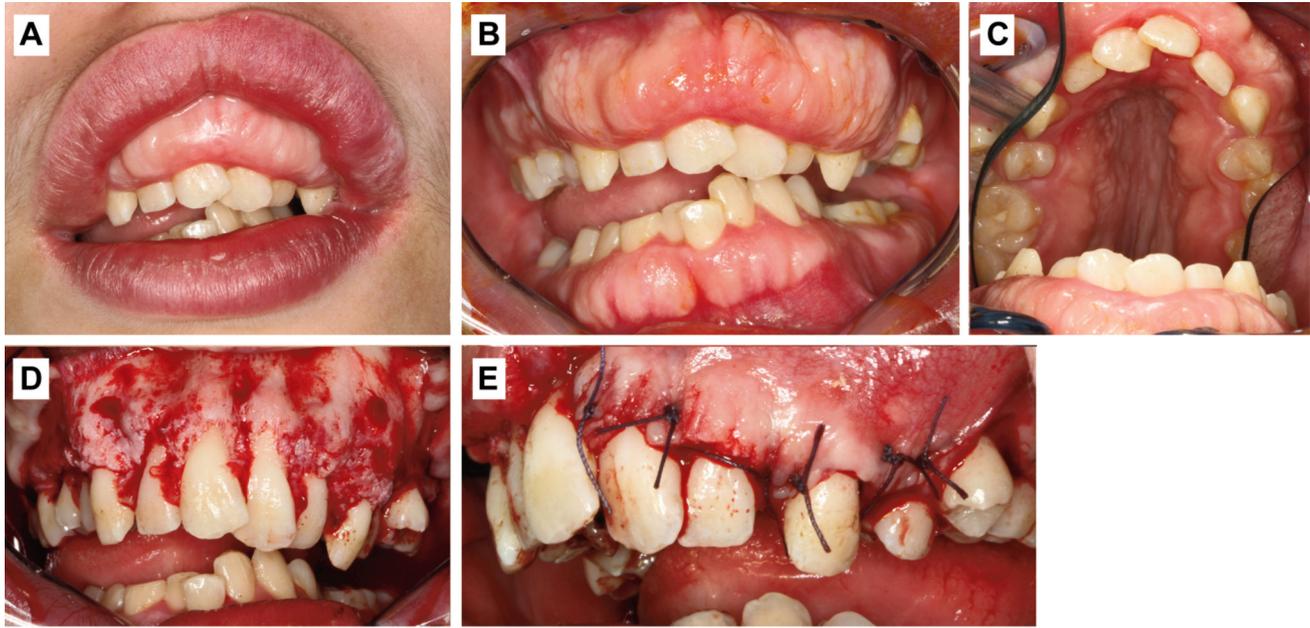


Figure 3. Oral findings of the patient with Proteus syndrome. (A) Open mouth at rest exposes mucosal hyperplasia of upper jaw. (B) Hyperplastic oral mucosa of both alveolar processes becomes apparent after lifting the lips. (C) The high-arched palate is not affected by the mucosal hyperplasia. (D) After lifting the mucosa, the prominent formation of the alveolar processes becomes apparent. There is periodontal bone loss in individual teeth. (E) Oral aspect after thinning of the hyperplastic connective tissue of the oral mucosa and contouring of the gingiva at the junction between the tooth crown and the tooth root.

Treatment. Debulking the extensive bony overgrowth of the frontal region was performed in general anesthesia. The bicortical extent of frontal bone hyperplasia was about 20 mm (Figure 2), as could be predicted from the proportions of the skull model (Figure 1D). The frontal sinuses were opened during bone debulking (Figure 2H). The defects were closed with bone chips and a galea-periosteal graft. Finally, the scalp was repositioned and fixed with sutures (Figure 2D). Wound healing was uneventful. One year later, the patient reappeared, this time to have removed the oral connective tissue hyperplasia, which caused both functional and aesthetic problems. In general anesthesia, vestibular pedicled mucoperiosteal flaps were raised and the alveolar processes exposed. The hyperplastic oral mucosa was thinned and the prominent undulating alveolar processes were modeled by leveling. Finally, the repositioned mucosa was contoured and fixed to the cementum-enamel border (Figure 3). Again, healing was uneventful.

Histology. The bones of the calvaria and the jaw were examined histologically. In both cases normal, lamellar bone was found with no evidence of inflammatory or dysplastic foci. The tissue samples of the oral mucosa revealed normal connective tissue with isolated nests of inflammatory cells.

Follow-up. The patient was satisfied with the oral and craniofacial treatment results and did not want further surgical

interventions. The patient was examined again 7 years later in another hospital because she was experiencing it increasingly different to swallow and her oral food intake was severely hampered. Current CT and magnetic resonance images of the neck revealed osseous constricted cervical spinal canal (C III-C VI) without evidence of myelon compression and no pathological myelon signal. However, the marked cervical lordosis and hypertrophic vertebral bodies were assessed to have an oropharyngeal mass effect.

Medical reports detail that she had a lockjaw at the time of inpatient admission for diagnosing causes of impaired food intake. Therefore, a transnasal endoscopy of the upper aerodigestive tracts was performed. Endoscopic examination showed significant external compression of the esophagus, possibly due to advanced anterior protrusion of cervical vertebrae. The mucous membranes of the esophagus were normal. Vascular malformations of the mucous membranes were not detected. The patient was recommended to have inserted a percutaneous gastric tube to secure gastrointestinal nutrition. Thereafter, the patient was lost for further follow-up.

Discussion

This report describes a remarkable growth excess in skull, cervical spine and oral mucosa and presents related regional pathologies. Successful local surgical treatment alleviated the patient from some physical disfigurement. Both bone surgery

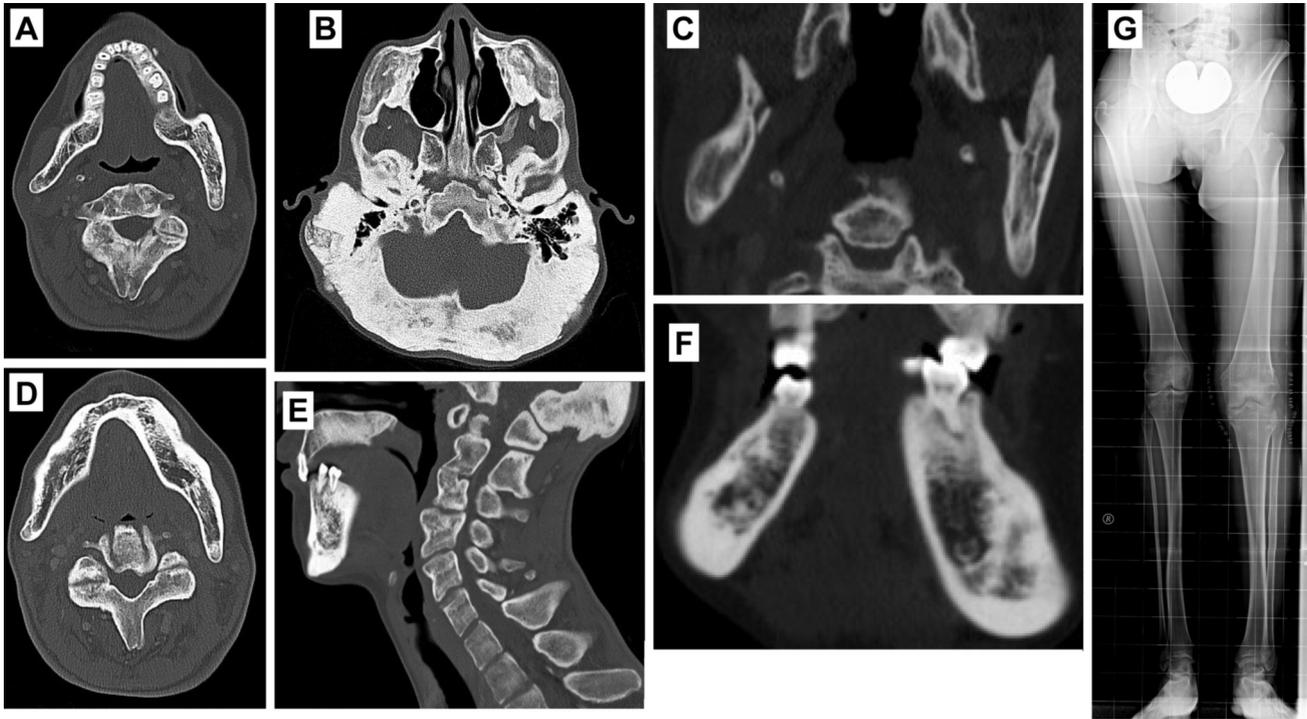


Figure 4. Radiological findings of the patient with Proteus syndrome in computed tomograms (A-F) and plain radiograph (G). (A) Asymmetrical and deforming hyperostosis of the mandible and cervical vertebral body (axial view). (B) Pronounced hyperostosis of the dorsal base of the skull and the zygomatico-maxillary complex. As shown in the 3D model (Figure 1B and D), the zygomatic arches are less affected by the hyperostosis than adjacent anterior and posterior bones. (C) Asymmetrically developed mandibular rami with differently developed mandibular foramina (coronal view). (D) The mandibular corpus is also developed asymmetrically, but the soft tissue coverage partially compensates for the asymmetry. The nerve canals are blurred (axial view). (E) Deformed and oropharyngeally protruding cervical vertebrae. Note the size ratio of the teeth to the surrounding jaw (sagittal view). (F) Asymmetrical mandibular body showing the mandibular canals. The canal on the left is significantly larger than on the right (coronal view). (G) Overview of the pelvis and lower extremities. The pelvis is inclined to the left side. The horizontal diameters of the long bones on the left are larger than those of the right.

and soft tissue modeling measures resulted in a permanent aesthetic and functional improvement in oral conditions and facial expression. However, as the disease progressed, local bone growth in the cervical spine probably led to severe impairment of oral nutrition.

Phenotype. Proteus syndrome is a progressive disorder that frequently comes to notice as asymmetric, dysproportionate overgrowth of tissues. The changes in size and shape typically arise shortly after birth of an apparently normally developed baby (16). The affected cells causing localized overgrowth may derive from any germline layer or combinations thereof. Somatic mutations arising early in ontogenesis are estimated to be the cause of the plethora of findings in Proteus syndrome (17). Progressive segmental overgrowth most commonly affects bones, skin, fat tissues, and central nervous system (18-27). Skeletal enlargements such as macrodactyly, vertebral anomalies (scoliosis), and hyperostosis usually get noticed firsts (1, 2, 8). However, asymmetric/dysproportionate development of vessels and

muscles are also characteristic features of the syndrome as are visceral findings such as cystiform pulmonary abnormalities (4). Furthermore, both regions of hyperplasia and hypoplasia may be noted in the same individual (28, 29) indicating that local overgrowth is a visually noticeable epiphenomenon of fundamental disruptions of cellular differentiation and cell metabolism (30).

Frequency. The rare occurrence of the disease and large differences in phenotype are major reasons why overviews of the phenotype were based on the evaluation of individual reports or case series small in number for long times (1, 4-8, 16, 18, 19). Only a few working groups report experience with diagnosis and therapy of Proteus syndrome based on larger numbers of cases (26, 31-33). Therefore, individual reports continue to help illustrate the phenotype and understand the disease. This assessment applies in particular to oral findings that have hardly been taken into account so far. However, the exclusion of cases previously erroneously diagnosed as Proteus syndrome in studies on overgrowth

Table I. *Historical scoring system to assess diagnostic features of Proteus syndrome. Minimum number of scoring points to diagnose Proteus syndrome is 13 [according to (5) and (7)].*

Feature	Points	Present case
Macroductyly and/or hemihypertrophy	5	Yes
Skin thickening (plantar and/or palmar cerebriiform hyperplasia)	4	Yes
Lipomas and subcutaneous tumors	4	No
Verrucous epidermal nevus	3	No
Macrocephaly or skull exostoses	2.5	Yes
Miscellaneous minor abnormalities	1	Yes
Total	19.5	12.5

syndromes is necessary to date because the overlap of certain findings in Proteus syndrome and related syndromes influences the initial assessment of the patients (18, 34). Classification suggestions are helpful for assigning a patient to a syndromic disease (Tables I, II and III).

Classification. Several attempts have been made to establish diagnostic criteria in Proteus syndrome (4 -8). An earlier classification assigns a numerical value to various findings, the sum of which must be greater than 13 (Table I). According to this classification, the presented case does not fulfill the diagnostic criteria. However, this early classification does not go into the fact that excessive growth of adipose tissue is just as much a part of the phenotype as a pronounced lack of adipose tissue (28, 29). The patient is extremely thin. A more recent classification (Table II) divides the relevant findings according to their diagnostic value in one general and three specific categories (8, 16). The categories assess the patient on different levels of knowledge, for which the course of the disease, quality and topography of the findings have their own and differently important meanings. In this classification, the dominant general category gives the disease a diagnostic spatio-temporal frame. This general category addresses predominantly, but not exclusively, the skeleton. Findings are assessed according to the time of first notice (postnatal), biological behaviour (progressive growth), and topography (asymmetry of findings, disproportional growth). The first specifying category A represents a single finding, that is the unusual hyperplasia of the connective tissue, predominantly arising in the foot sole (8). In further explanation of the diagnostic criteria it is admitted that skin changes of this type can also occur in other parts of the body and used diagnostically, but are less frequently recorded (16, 31). Findings now known as cerebriiform cutaneous tissue nevus (CCTN) were already listed as characteristic palmar features of the syndrome in 4 of 5 cases in a publication where the eponymous designation of the disease was introduced (4). These cutaneous signs were

called CCTN because of the similarity between the affected skin and the surface of the exposed brain. Until recently, the “gyrated (skin) surfaces” (35) or “gyriform masses” (36) were so characteristic for Proteus syndrome that evidence of CCTN - in conjunction with the general category - was conclusive for clinical diagnosis of Proteus syndrome (8, 37). Current studies show this specificity of the finding is not valid (38). However, the recently announced limited diagnostic specificity does not affect the importance of the finding for orienting clinical examinations in the event of a suspected Proteus syndrome (39). CCTN is better assigned as connective tissue *malformation* (40) and was detected in 97% of cases (feet) and 28% (hands), resp. (31). The categories B and C list several findings. However, findings in categories B and C only contribute to the diagnosis if all individual findings have been registered in the respective sub-category. According to this classification, the diagnosis of Proteus syndrome is dominated by fulfillment of the diagnostic criteria according to the general category and category A (16). Applied to the presented case, despite recording numerous groundbreaking findings in categories B and C, the total number of individual findings does not fulfill all items of the sub-categories. However, category A criterion is met, and the general characteristics apply to the case.

Genetics. Prevalence of Proteus syndrome (Online Mendelian Inheritance in Man No. 176920) is estimated 1:1,000,000. However, some authors have expressed doubts about prevalence estimates because oligosymptomatic patients can escape diagnosis (41). Male-to-female ratio is 1.9:1. Proteus syndrome is a sporadic disease caused by somatic mutations (15, 17). It is assumed that Proteus syndrome belongs to the heterogeneous group of sporadic genetic diseases characterized by postzygotic mutations surviving by mosaicism, which, as germ cell mutations, are lethal (42, 43).

About 90% of cases carry a somatic activating mutation (c.49G→A,p.Glu17Lys) in the oncogene AK strain transforming 1 [(AKT1), cytogenetic location: 14q32.33], encoding the AKT1 kinase (previously used synonym: RAC-alpha serine/threonine-protein kinase). AKT1 is an enzyme known to mediate cell proliferation and apoptosis (16, 44). However, it has not been yet possible to establish a correlation between the mutation status of the tissue and the lesions in the syndrome (45). Recent studies show allelic heterogeneity of Proteus syndrome in AKT1 mutations, so lack of evidence of the characteristic mutation should no longer be interpreted as an exclusion diagnosis in a potential case of Proteus syndrome (46). The patient’s genetic status was not examined because the patient had been treated before the characteristic mutation was identified.

Skull. The local osseous overgrowths should be described as ‘hyperostosis’ not as exostosis or osteoma (8). However, the

Table II. Current clinical diagnostic criteria to establish Proteus syndrome diagnosis [according to (16)]*.

General criteria (Mandatory)	Category A	Category B	Category C
Mosaic distribution of lesions	Cerebriform connective tissue nevus (CCTN)	Linear epidermal nevus	Dysregulated adipose tissue (either of the following): Lipomatous overgrowth and/or Regional lipatrophy
Sporadic occurrence		Asymmetric, disproportionate overgrowth** (≥1 of the following): Limbs Hyperostosis of the skull Hyperostosis of the external auditory canal Megaspondylodysplasia (i.e., abnormal growth of vertebrae) Viscera: spleen/thymus	Vascular malformations (one of the following): Capillary malformation Venous malformation Lymphatic malformation Bullous pulmonary degeneration
Progressive course		Specific tumors with onset before the second decade (either of the following): Bilateral ovarian cystadenoma Parotid monomorphic adenoma	Facial phenotype (all of the following): Dolichocephaly Long face Downslanting palpebral fissures and/or minor ptosis Depressed nasal bridge Wide or anteverted nares Open mouth at rest

*For clinical diagnosis of Proteus syndrome, the following combinations of findings are the minimum: ALL of the general criteria AND specific criteria from categories A-C: One from category A, OR two from category B, OR three from category C. **The authors of the classification emphasize that asymmetric, disproportionate overgrowth should be carefully distinguished from asymmetric, proportionate, or ballooning overgrowth.

term ‘exostosis’ is still used for these bone changes (Tables I and III) (47). Modeling osteotomy is an essential tool for reducing the facial disfigurement caused by excessive bone growth. Approaches and osteotomy techniques are based on the principles of craniofacial surgery. In the presented case, noticeable protrusions of the bone had to be corrected. The overall increased skull growth and its effects on the facial type were not influenced by the measure.

Craniofacial bone reduction. The use of removed bone to contour the calvaria is not recommended because it is suspected the reuse of the lesion bone increases the risk of recurrence. If the removal of calvarial bone leads to defects, intact bone regions should be selected as the donor region (13). In the present case, chips of resected bone segments were used to cover the opened roof of frontal sinuses. During the observation interval, there was no recurrence of excessive bone growth in the contoured frontal region. However, the recipient site of the osteoplasty consisted of the residual bone that had given rise to the excessive and disfiguring skeletal growth.

Skin. Skin findings are important in diagnosing the syndrome. Linear lesions of an epidermal nevus, teleangiectatic nevi or vascular lesions were recorded in more than 60% to 88% of cases (26) and can be very pronounced (47). Hyperplasia of

connective tissues of feet soles is considered a hallmark of Proteus syndrome (see “classification”). The lesion is variable in size and may create a localized cushion-like excess of soft tissue (17). Also called “moccasin” lesions (17), the frequent but not obligatory finding arises uni- or bilaterally (31). Development of lipoma is recorded in about 9 of 10 affected individuals (26, 31). On the contrary, dermal hypoplasia was recorded in 22% of patients (31).

Oral soft tissue. While malformations and tumors of the skin in Proteus syndrome have been described more frequently, oral manifestations have been noted only rarely. For example, dental manifestations of Proteus syndrome are not mentioned in a detailed review on diagnosis of oral findings of syndromic rare diseases with craniofacial manifestations (48). Gingival hyperplasia was noted by Arendorf and Henslo (49). In their case, local soft tissue overgrowth had covered several maxillary teeth. Gingivectomy was performed and permanently achieved both contouring of the gingiva and occlusal contact of teeth. Histological examination confirmed regular epithelial differentiation with mature bundles of collagenous fibres. Clusters of fibroblasts and chronic inflammatory cells were embedded in the connective tissue (49). Another report describes unilateral muco-gingival hyperplasia of the mandible. Biopsy of the oral soft tissue revealed fibromatosis gingivae (50). Obviously, soft tissue findings of the oral cavity are rarely

Table III. Literature review of Munhoz et al. (32) on oral and maxillofacial findings in Proteus syndrome derived from 14 cases. Findings observed in the presented case are highlighted in bold.

Extraoral findings	Intraoral findings	Imaging findings
Epidermal nevus Hemifacial/ specific bone hypertrophy Craniofacial asymmetry Presence of exostoses	Impacted teeth Malocclusion (<i>i.e.</i> : dental crowding, dental rotation, asymmetric occlusion) Dental ectopia Asymmetric enamel hypoplasia	Panoramic radiography: - Dental agenesis and/or ectopia, impacted teeth, roots dilacerated and/or resorption - Mandibular hemihypertrophy - Enlargement of mandibular canal**, mandible body**, ramus, condyle**, mental foramen* - Asymmetric dental growth and maturation Computed tomography: - Degenerative changes or enlargement of the temporomandibular joint Exostosis Lateral cephalometric radiograph - Prognathism or retrognathism (Maxilla and/or mandible) - Vertebral enlargement* Magnetic resonance imaging - Fibrofatty facial mass infiltration - Primary expansion of bone marrow and bone hypertrophy* - Hyperostosis*
Mandibular retrusion or prognathism Open mouth at rest Long face Hypertelorism	Teeth agenesis Shape changes in hard palate, mandible, maxilla Asymmetric macroglossia Exostosis , osteoma	
Macrocephaly	Midline deviation Unusual frenula	

*Findings revealed on CT and identified on skull model. **Unilateral or asymmetric.

noted in patients with Proteus syndrome. For example, the detailed analysis of oral findings in the case of significant hyperplasia and deformation of the calvarial and facial bones revealed malocclusal of teeth and tooth root resorption but no hyperplasia of the gingiva (35). A systematic review of published data on maxillofacial manifestations of Proteus syndrome with special consideration of oral manifestations (32) (Table III) describes gingival hyperplasia in only two cases (49, 50) based on 14 studies used for this evaluation. This overview can be supplemented by further two reports on gingival hyperplasia in Proteus syndrome (36, 51). However, no histological findings are detailed in either report.

Further observations refer to unusually high-set frenula, which can cause diastema mediale or develop bifid (47). There are also individual reports of unilateral hyperplasia of the tongue (21, 51, 52).

Teeth. Occasionally, the patient's teeth are conspicuous due to crowding of occlusion disorders. Teeth in Proteus syndrome are usually of normal size (49), an important difference to hemifacial hyperplasia patients who often have macrodontia (52). Tooth development can be influenced in unilaterally affected jaw sections, so a comparison of the jaw sides may show different stages of development (35). The different sizes within a jaw can cause considerable vertical difference in the occlusal plane between affected and unaffected jaw sections (52). In the presented case, the incorrect occlusion of the rows of teeth was associated with

an asymmetrically developed bilateral and bimaxillary hyperostosis. Other reports detail enamel hypoplasia (53, 54). Tooth retentions are described for patients with Proteus syndrome, as well as agenesis of teeth (32). In summary, the reports on dental findings in Proteus syndrome are rare and so far, findings are not specific (32).

Jaws. Hyperplasia of the jaws is usually unilateral in Proteus syndrome (3, 12, 51). Skeletal overgrowth can affect the entire side of one or both jaws or only sections of the respective bone, for example the condylar process (51, 52, 55, 56). Functionally effective, symmetric underdevelopment of the mandibular corpus was also reported (57). In the present case, both jaws are substantially oversized and slightly asymmetrical. The soft tissues proportionally cover the bone and extends evenly in regions with hyperostosis. The association of soft tissue excess, *e.g.* CCTN, and skeletal hyperplasia and/or deformity is characteristic in the distal contact areas of extremities in Proteus syndrome (14), but is not a frequent sign in the skull. For example, oropharyngeal soft tissue hyperplasia developed without hyperplasia of the adjacent facial bone (36).

In the present case, the palate was high arched. High arched palate is a frequent finding in several syndromes. High arched palate can be missing in patients with jaw overgrowth (51, 52). Open bite is a rare finding independent of dental crowding (52, 57). Enlargement of inferior alveolar nerve and mandibular canal was noted in Proteus syndrome (52). However, an

enlarged mandibular nerve canal on plain skull X-ray or CT is not proof of an enlarged nerve. Enlarged mandibular canals have been demonstrated for other syndromes, particularly in patients with neurofibromatosis type 1 (NF1) (58).

Localized bone growth was observed in the alveolar process of the mandible (3). However, these bone findings were addressed as alveolar 'exostoses' (3), while in the present case the alveolar processes appear proportionally enlarged or vestibularly protruded.

In the further course the patient had apparently experienced considerable restrictions in opening the lower jaw. These findings were only known from a later medical report. A cause for the functional impairment is not known. Restricted mouth opening without evidence of a causal skeletal condition has been reported occasionally (32). A maxillary tumor of unknown origin in the left maxilla was reported (35) and a case with teeth agenesis and odontogenic fibroma (47). The detection of AKT1 mutation in a dental cyst of a Proteus patient proved first evidence of association between the disfiguring disease and an oral dysontogenetic finding (47).

Spine and swallowing disorder. Deformations of the spine as a whole and deformations and enlargements of one or more vertebral bodies belong to the skeletal phenotype of Proteus syndrome (59). Orthopedic surgical measures are necessary in cases, for example, when spinal compressions lead to functional failures (60). In the case presented, the deformed and enlarged cervical spine did not have any functional impairment of the swallowing function during the craniomaxillofacial surgery phase. The reported significant swallowing disorder did not occur until several years later. The cause of the swallowing disorder was suspected to be the progressive growth of the vertebral bodies with compression of the esophagus. However, soft tissue masses can make speaking and swallowing difficult and require surgical intervention (36, 61).

Further rare findings in present case. The patient has some findings that have been rarely or not at all reported in connection with Proteus syndrome.

Diabetes mellitus. The patient developed type I diabetic mellitus. The association of Proteus syndrome and diabetes is not listed in reviews on the syndrome (16), nor in more recent papers based on the genetic characterization of AKT1 mutation in the disease (46). Syndromal associations with diabetes mellitus have been described for mutations of the AKT2 gene (62). Polyuria in Proteus syndrome was reported occasionally (6).

Likewise, Hashimoto thyroiditis is not a feature that is included in the plethora of the Proteus syndrome findings. Association of Hashimoto thyroiditis with syndromes has been reported on various occasions, for example in Bannayan-Riley-Ruvalcaba syndrome (63) or in NF1 (64).

The hyperostosis of the external auditory canal is considered rare in Proteus syndrome (9). However, the evidence of this ossification disorder in patients is an important indicator to confirm the suspicion in candidates of Proteus syndrome diagnosis (3, 9).

The influence of the disease on the skeletal system causes characteristic localized disproportionate growth of single or multiple bones. However, height attainment of patients with Proteus syndrome is usually normal (9). The patient's bones have grown disproportionately at several sites. She had several orthopedic operations to correct skeletal disproportions of the hip and lower extremity. The measures apparently resulted in a shortening of the lower left extremity, which was mainly affected by overgrowth. However, the patient has grown unusually tall. It can be assumed that this unusual height is related to the underlying disease. However, no further endocrinological examinations were carried out during the surgical therapy in order to rule out defined causes of skeletal growth errors. Above average growth has occasionally been reported in patients with Proteus syndrome (13).

Proteus syndrome and NF1. In the scientific-historical discussion of the Proteus syndrome, the distinction from NF1 is of particular importance because for many years the so-called elephant man had been diagnosed as suffering from neurofibromatosis (5). By re-evaluating known findings, Tibbles and Cohen (65) and Cohen (2) have identified the Proteus syndrome as very likely the diagnosis of this historical case. Reliable diagnostic criteria were defined in consensus for diagnosing NF1, which, with some modifications and corrections, have withstood the test of time (66). In addition, NF1 is an autosomal dominant hereditary disease, the gene locus of which is known and can be determined in over 90% of cases (67). The present patient did not have any of the stigmata of integument that guide the diagnosis of NF1 (66). The application of strict diagnostic criteria to classify a patient with Proteus syndrome is essential. Failure to consider the minimal spectrum of accepted diagnostic findings (9) can lead to erroneously or at least unfounded application of the diagnosis (3, 21, 26, 33, 43).

Conclusion

Proteus syndrome is a disease that can affect many organs and regions of the body. In the case of skeletal overgrowth, surgical measures can reduce the degree of disability and alleviate the symptoms in individual cases. Oral findings associated with the disease have so far been rarely reported in Proteus syndrome. Conspicuous oral soft tissue overgrowths can cause functional and aesthetic impairments that can at least partially be treated surgically. The application of local measures must consider that many patients have to

struggle with consequences of their genetic disposition that lie outside the respective therapeutic field (68). As can be seen in the presented case, the general diagnostic criteria (16), in particular the progressive course of the disease, are a decisive factor in the patient's quality of life (68).

Conflicts of Interest

The Author states that there are no conflicts of interest regarding the publication of the study.

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