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REVIEW ARTICLE

Maxillofacial manifestations of Proteus syndrome: a systematic review with a case report

Luciana Munhoz[1] · Emiko Saito Arita[1] · Danielle Ayumi Nishimura[1] · Plauto Christopher Aranha Watanabe[2]

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Abstract

Objectives Proteus syndrome (PS) is an extremely rare disorder with asymmetric and disproportionate bone overgrowth. Craniofacial abnormalities in PS are less frequent than skeletal abnormalities. Although there are recognized oral and maxillofacial manifestations of PS, few case reports describing these manifestations are available. Thus, the objective of this systematic review and case report is to describe oral and maxillofacial manifestations of PS and to report a PS case.

Methods A 31-year-old male presented with restricted mouth opening and pain during mastication. A panoramic radiograph and an occlusal radiograph were obtained. Reports with relevant keywords were assessed. Data were summarized and demonstrated using a critical appraisal checklist for case reports.

Results The panoramic radiograph demonstrated unilateral overgrowth of the mandible, impacted teeth, and deciduous prolonged retention. Thirteen PS case reports were identified.

Conclusions Proteus syndrome oral and maxillofacial manifestations may include dental agenesis, impacted teeth, malocclusion, asymmetric dental growth and maturation, frontal line displacement, asymmetric tongue enlargement, mandibular hemihypertrophy and asymmetry, presence of exostoses/hyperostosis, degenerative changes in the temporomandibular joint, alterations of maxillary and mandibular vertical and/or horizontal growth, and enlargement of mandibular canal and foramen. The PROSPERO systematic review registration number is CRD42019140942.

Keywords Diagnostic imaging · Oral pathology · Proteus syndrome · Jaws · Maxilla · Mandible

Introduction

Proteus syndrome (PS) is an extremely rare disorder with unknown etiology, first described by Cohen and Hayden in 1979 [1, 2]. A few years later, the name "Proteus" was given by Wiedemann, in reference to the Greek sea god Proteus, who has the ability to change his shape to avoid his capture [3]. The syndrome is defined as an overgrowth syndrome, which is a result of a mosaic activation of a mutation of AKT1 [4].

Proteus syndrome manifestations include vascular malformations, asymmetric and disproportionate overgrowth with skeletal defects, dysregulated adipose tissue, cerebriform connective tissue nevi and epidermal nevi, lung cysts, development of specific types of neoplasms (usually before the second decade of life, such as ovarian cystadenomas and parotid monomorphic adenomas), increased risk of deep vein thrombosis, and a facial phenotype, which is associated with intellectual disability and eventually brain malformations [2]. As the presentation of the disorder is highly variable, diagnostic criteria were developed to identify PS patients [5].

Craniofacial abnormalities in PS are progressive and less frequent than skeletal abnormalities; the syndrome often leads to exostosis and/or overgrowth of membranous bone, producing dentofacial deformities and malocclusion [6]. When brain malformations are present, which can result in seizures and/or intellectual disability, a typical facial phenotype can be observed and includes dolichocephaly, a long face, low nasal bridge, wide or anteverted nares,

✉ Luciana Munhoz
dra.lucimunhoz@usp.br

[1] Department of Stomatology, School of Dentistry, University of São Paulo, 2227 Lineu Prestes Avenue, São Paulo, SP 05508-000, Brazil

[2] Department of Stomatology, Public Oral Health, and Forensic Dentistry, Ribeirão Preto Dental School, University of São Paulo, Café Avenue, Ribeirão Preto, SP 14040-904, Brazil

downslanting palpebral fissures and/or minor ptosis, and an open mouth at rest [5].

Abnormal development of dentition, teeth agenesis and ectopia, gingival hypertrophy, crowding, malocclusion, multiple frenulae, gingival hypertrophy, a high arched palate, an asymmetric hypertrophied tongue, and enamel hyperplasia are usual oral manifestations of PS [6]. Although there are recognized oral and maxillofacial manifestations associated with PS, few case reports describe specific oral manifestations, and no systematic reviews are available.

The objective of this paper is to describe oral manifestations of PS in case reports, thus summarizing these features and providing dental professionals with an overview of the main findings related to PS.

Furthermore, a case of PS is demonstrated to illustrate the literature findings and PS maxillofacial-oral manifestations detected by imaging examinations was described.

Materials and methods

For the systematic review, the following questions were addressed:

1. What are the intraoral manifestations of Proteus syndrome in the literature?
2. What are the maxillofacial manifestations of Proteus syndrome in the literature?
3. What are the imaging examinations and imaging features of Proteus syndrome in the literature?

Proteus syndrome case reports were selected using PubMed, Embase (Excerpta Medical Database), Cochrane Central Register of Controlled Trials, Scopus, Web of Science, and Google Scholar databases. These databases were searched for English language publications until July 2019. The inclusion criteria aimed to select PS case reports that described maxillofacial-oral manifestations. Original articles and literature reviews were excluded, as well as PS-like syndromes. Articles unavailable as full text in the authors' university library system were requested directly from the corresponding authors and excluded if there was a lack of response. The qualitative assessment of the case reports was performed according to the Joanna Briggs Institute (2017) critical appraisal checklist for case reports [7]. The checklist consists of eight questions. Checklist items were marked as "yes, no, unclear or not applicable".

The keywords (Medical Subject Heading terms) were Proteus syndrome AND oral diagnosis; Proteus syndrome AND oral pathology; Proteus syndrome AND oral cavity; Proteus syndrome AND jaws; Proteus syndrome AND maxilla; Proteus syndrome AND mandible; Proteus syndrome AND facial bones.

Papers not available on the internet, the reviewers' university library, or the national cooperative library system were requested from the authors. If there was a lack of response from the authors, the case reports were excluded.

Case description

A 31-year-old male patient was referred to the dentistry service (Faculdade de Odontologia de Ribeirão Preto, São Paulo, Brazil) due to pain during mastication and gingival inflammation. The extraoral examination showed limited mouth opening and presence of facial asymmetry, with mandible overgrowth on the left side. Intraoral examination revealed poor oral hygiene associated with gingivitis and caries. The patient was partially dentate. The patient's medical history included thrombocytopenia, medullar hypoplasia, severe scoliosis, hypertension, and gastritis. At the consultation, the patient was using a wheelchair. The patient was already diagnosed with PS by the medical team at Hospital das Clínicas de Ribeirão Preto (Faculdade de Medicina de Ribeirão Preto, São Paulo, Brazil).

The panoramic radiograph (Fig. 1) demonstrated a mandibular asymmetry (an overgrowth on the left side), with multiple retained teeth, mainly on the overgrown side. On the left side, the retained teeth were located near the angle of the mandible and a deciduous tooth was maintained. The occlusal radiograph (Fig. 2) showed anterior teeth misplacement.

As a complement to the panoramic radiograph, an open and closed mouth temporomandibular joint radiograph was requested. In this radiograph, the left mandible head and condyle were larger than the right mandible head and condyle. Restricted mouth opening was noted on both sides. The mandibular fossa was depthless on the left side when compared to the right side, in concordance with the mandible head anatomy (Fig. 3).

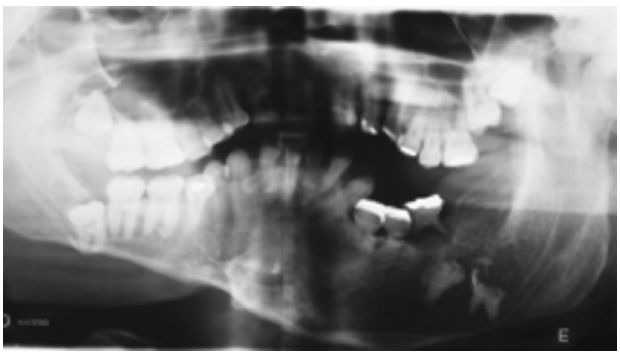

Fig. 1 Panoramic radiography of a patient with Proteus syndrome. Note the asymmetric overgrowth, irregular occlusal plane, and the tooth retention

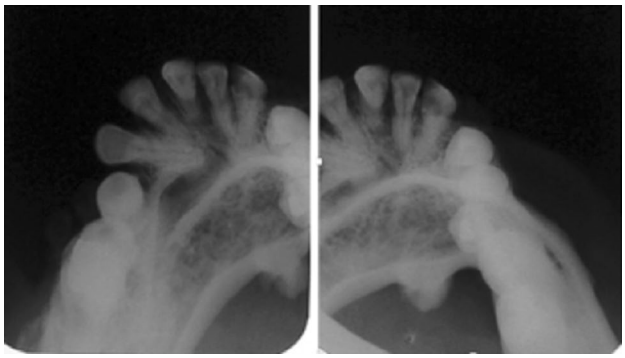

Fig. 2 Occlusal radiograph of the case. Anterior teeth displacement is observed

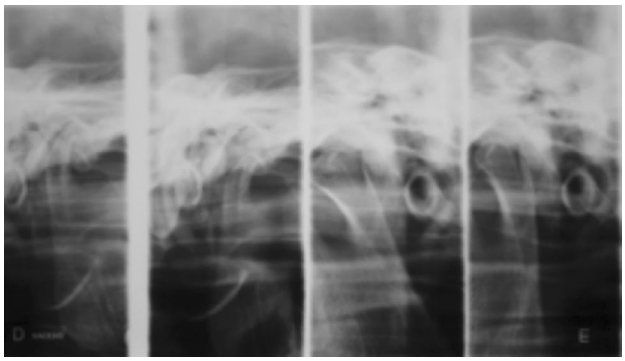

Fig. 3 Temporomandibular joint radiograph of the case. Note that the left mandible head and condyle is larger than right mandible head and condyle

Results

The literature search identified 14 English language articles [6, 8–20] with 14 cases containing descriptions of PS oral manifestations. The oldest manuscript was from 1994 [19], and the newest was from 2015 [6]. Most of the cases were from female patients [6, 8, 9, 11–16, 18, 20]. The search results and summarized data from the selected PS case reports are available in Table 1. Literature review flow chart is available on Fig. 4.

The qualitative assessment of the case reports included is demonstrated in Table 2. Question number seven of the qualitative assessment checklist was marked as "not applicable" for all the articles cited in this review, as this question relates to a new condition or drug treatment [7]. The most frequent "no" answer was regarding to the item of the description of interventional procedures and post-intervention procedures [8, 10, 11, 16, 20]. The main focus of the papers was the imaging features of patients with PS, not treatment, with the exception of one paper [20]. One report also did not describe the diagnostic methods [19].

Regarding the oral manifestations of PS, a summary of the main intraoral and extraoral findings, as well as the imaging examinations requested for each patient, is available in Table 3. The findings reported by the investigators are in Fig. 5.

Table 1 Case reports selected considering the inclusion criteria

Authors	Year	Main subject	Age and gender	Country
Valéra et al. [6]	2015	Case report with a dental cyst	07, female	France
Yilmaz et al. [8]	2013	Radiographic manifestations in temporomandibular syndrome	33, female	Turkey
Sakamoto et al. [9]	2010	Craniofacial hypersostosis	Case 1: 06, female Case 2: 56, male	Japan
Nogueira et al. [10]	2007	Mandibular retrusion	17, male	Brazil
Korbmacher et al. [11]	2005	Dentomaxillofacial imaging	07, female	Germany
Adolphs et al. [12]	2004	Craniofacial hypersostosis	17, female	Germany
Rao and Vohra [20]	2003	Gingival hyperplasia	12, female	India
Becktor et al. [13]	2002	Craniofacial development	13, female	Denmark and Sweden
Gilbert-Barness et al. [14]	2000	Craniofacial hypersostosis, multiple meningiomas	21, female	USA
DeLone et al. [15]	1999	Magnetic resonance imaging features	05, female	USA
Pinto et al. [16]	1998	Case report with severe mandibular hemihypertrophy	42, female	UK
Arendorf and Hanslo et al. [17]	1995	Case report with gingival hyperplasia	09, male	South Africa
Mason and Roberts [18]	1995	Enamel hypoplasia	11, female	UK
Smeets et al. [19]	1994	Regional manifestations	07, male	Canada

Authors of the reports, year of publication, main subject, age and gender of the patient with PS and authors 'country origin

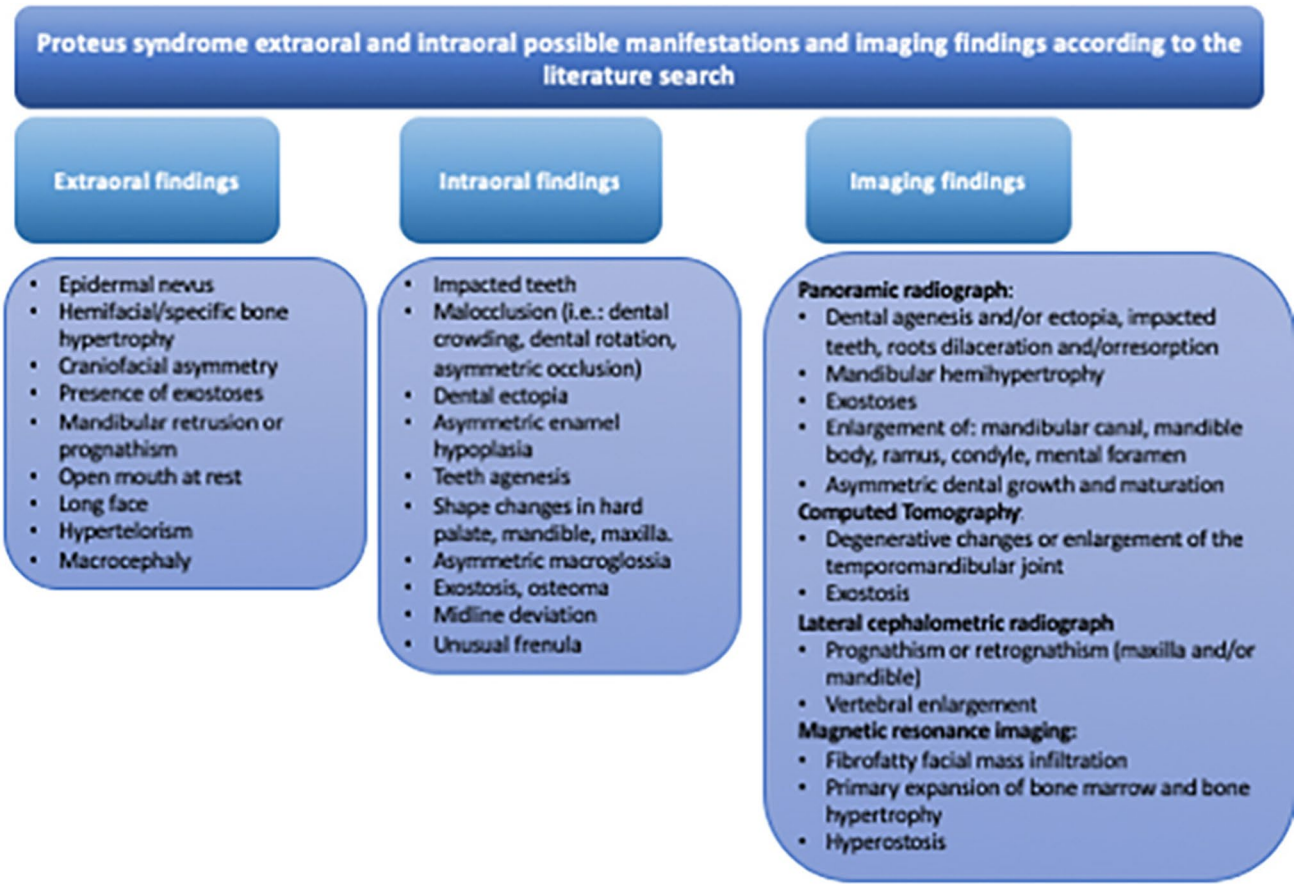

Fig. 4 Literature review flow chart

Discussion

As PS has highly variable clinical features, with mosaic lesion distribution and sporadic occurrence [21], leading to misdiagnosis as other overgrowth syndromes [5], the diagnosis depends heavily on clinical evaluation and imaging findings [22], as well as the accurate assessment of each diagnostic criterion [2, 5, 21]. It is important that dental professionals are aware of PS oral manifestations, as PS patients strongly need dental care such as orthodontic, surgical, periodontal, and restorative treatments. Although PS craniofacial manifestations are not frequent [22], craniofacial hyperostosis is observed in approximately 30% of PS patients and dental anomalies are observed in 18.6% of patients [23]. The disorder affects more male than female patients [21], although manuscripts which reported PS oral manifestations had more females.

Proteus syndrome overlaps with other overgrowth disorders, such as Klippel–Trénaunay syndrome, hemihyperplasia-multiple lipomatosis syndrome [24], type 1 neurofibromatosis, Parkes–Weber syndrome, Maffuci's syndrome, Ollier's dyschondroplasia, Bannayan-Zonana syndrome, and encephalocraniocutaneous lipomatosis [25], all of which may be considered in the differential diagnosis of PS. An important point that differentiates PS from other overgrowth syndromes is the asymmetry of the lesions [5], which was seen in the case reports and in our case, mostly regarding asymmetric enlargement of the mandible or maxilla or asymmetric dental maturation. In our case, the mandible was asymmetric, with an overgrowth in the left side, resulting in malocclusion and an irregular occlusal plane.

Conventional radiographs, particularly panoramic radiographs, are often requested as the first imaging examination to investigate the dentomaxillo status of PS patients [6, 8, 10, 11, 13]. Panoramic radiographs provide a large amount of information, such as the presence of impacted teeth [11], teeth agenesis [6], root dilaceration [8] and resorption, [11] ectopic eruption of teeth, asymmetric dental maturation [11, 13], and asymmetric enlargement of the maxilla or mandible [8, 13].

Further imaging examinations, such as lateral cephalometric radiographs or computed tomography are needed to plan interventional approaches. Lateral cephalometric radiographs are useful to determine orthodontic treatment and demonstrate prognathism or retrognathism, as well as asymmetric mandible overgrowth in PS patients [11, 13].

Table 2 Risk of bias assessment according to "The Joanna Briggs Institute (2017)" critical appraisal checklist for case reports [7]

Author	1—Were patient's demographic characteristics clearly described?	2—Was the patient's history clearly described and presented as a timeline?	3—Was the current clinical condition of the patient on presentation clearly described?	4—Were diagnostic tests or methods and the results clearly described?	5—Was the intervention(s) or treatment procedure(s) clearly described?	6—Was the post-intervention clinical condition clearly described?	7—Were the adverse events or unanticipated events identified and described?	8—Does the case report provide takeaway lessons?
Valéra et al. [6]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Yilmaz et al. [8]	Yes	Yes	Yes	Yes	No	No	NA	Yes
Sakamoto et al. [9]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Nogueira et al. [10]	Yes	Yes	Yes	Yes	No	No	NA	Yes
Korbmacher et al. [11]	Yes	Yes	Yes	Yes	No	No	NA	Yes
Adolphs et al. [12]	Yes	Yes	Yes	Yes	No	No	NA	Yes
Rao and Vohra [20]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Becktor et al. [13]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Gilbert-Barness et al. [14]	Yes	Yes	Yes	No	Yes	Yes	NA	Yes
DeLone et al. [15]	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes
Pinto et al. [16]	Yes	Yes	Yes	No	No	No	NA	Yes
Arendorf and Hanslo et al. [17]	Yes	Yes	Yes	No	Yes	No	NA	Yes
Mason and Roberts [18]	Yes	Yes	Yes	No	Yes	No	NA	Yes
Smeets et al. [19]	Yes	Yes	Yes	No	No	No	NA	Yes

NA not applicable

Table 3 Case report summary pertaining to oral manifestations of Proteus syndrome. Main features described in the case report, extraoral and intraoral examination findings and imaging findings of the cases

Author	Main features described	Extraoral examination findings	Intraoral examination findings	Imaging findings
Valéra et al. [6]	Dental cyst associated to an impacted tooth	Bump in the left parietal bone; epidermal nevus in the neck	Malocclusion (increased overjet, dental crowding, lingual posterior crossbite, dental ectopia and rotation), enamel hypoplasia and teeth agenesis and impactation	PR: dental agenesia (canine and premolar); radiolucent unilocular lesion with well-defined margins associated with the crown of the impacted right second premolar, without expansion of the cortical bones
Yilmaz et al. [8]	Asymptomatic condyle malformation, craniofacial, oral and dental findings	Pronounced hemifacial hypertrophy of the left side and abundant hair growth in the chin and cheek area on the affected side	High arched palate and enlargement of the left mandibular posterior alveolar bone; gingival hyperplasia, unilateral enlargement of the tongue on the affected side	In the affected side: PR: mandibular hemihypertrophy and hyperostoses; enlarged tuber maxilla; alveolar bone loss; dilaceration of the roots; condyle malformation CT: extensive degenerative changes in TMJ with pseudoarticulation of the coronoid process; new bone formation in the occipital and temporal region Open–closed lateral TMJ radiograph: limitation of condyle movement
Sakamoto et al. [9]	2 cases of Proteus syndrome: 1 with recurrence after the eliminations of the hyperostosis; 1 untreated	Case 1: Cranium asymmetry, hyperostosis in the left parietal and orbit Case 2: hard masses in the mandible, maxilla, zygoma, frontal, and left occipital regions	Case 1: intraoral examination not reported Case 2: Prominences in maxilla and mandible	CT (both cases) examinations of both cases demonstrated and allowed the measurement of the hyperostosis areas
Nogueira et al. [10]	Apnoea and mandibular retrusion as an uncommon finding in Proteus syndrome	Dolichocephaly pattern, mandibular retrusion, hyperostosis in the skull	Malocclusion, jaw atresia causing severe crowding and anterior open bite, poor oral hygiene, gingival inflammation, teeth in infraocclusion	PR: evidenced malocclusion LCR: overgrowth of the upper cervical vertebrae Skull CT: vertebral oversize, hypertrophy of lower turbinate and left condyle malformation
Korbmacher et al. [11]	Emphasis in the radiographic imaging findings including orthodontic records	Calcifying bonelike tumors of the subcutis near the root of the nose and left parieto-frontal, a tumor of the soft tissue of unknown origin in the left maxilla, left sided hemifacial hypertrophy with an asymmetry to the right side; long-face syndrome, open mouth at rest	Multiple orofacial dysfunctions; late mixed dentition, class III malocclusion with an asymmetric occlusion due to skeletal midline shift to the right with a reduced overjet and overbite	PR: asymmetric dental growth and maturation; impacted tooth, no signs of abnormal root resorption LCR: cephalometric analysis revealed a prognathism of the maxilla and mandible, mandibular asymmetry FCR: mandible displacement of 4.5 mm to the right compared with the frontal midline, hypertrophy of the left side of the calvarium and the ramus and body of the mandible were enlarged. The frontal sinus could not yet be detected

Table 3 (continued)

Author	Main features described	Extraoral examination findings	Intraoral examination findings	Imaging findings
Adolphs et al. [12]	Craniofacial hypersostosis surgery approach	Right side frontal, temporal and parietal bones, the greater wing of the right sphenoid, right zygoma, right maxilla and right mandible were enlarged in comparison with the structures on the left side	The occlusal plane was tilted down to the right due to enlargement of the right zygoma and local hyperostosis of the alveolar crest of the right maxilla. The patient had a compensated Angel's class I occlusion	Conventional radiographs and CT showed the enlargement of the comprised bones
Rao and Vohra [20]	Gingival hyperplasia and other findings	Enlargement of the lower right lip and right cheek	Lower right hyperplasia in gum	Plain radiographs: exostosis in the left parieto-occipital region PR: malocclusion, alveolar bone enlargement
Becktor et al. [13]	Craniofacial development and interventions of a Proteus syndrome case with full history since 6 months	Enlargement of the left facial osseous and soft tissue. The left ear was slightly posteriorly positioned. Exostosis were present in the parietal lesion	Secondary retention of the left first and second permanent molar in the mandible. Normal dental anatomy (size, shape, and minerali- zation) including gingival tissue. The left side of the tongue was symmetrically enlarged	PR: dental growth and maturation between the left and right side were significantly different; development was slightly retarded on the right and advanced in several teeth on the left side. Dental agenesis (left lower third molar), ectopic eruption, idiopathic root resorption, and various anatomic malformations were observed. Enhanced maxillary and mandibular vertical growth of the left alveolar processes were present. The left condyle, ramus, and body and the left mandibular canal and mental foramen were enlarged LCR: cephalometric analysis showed prognathism of the maxilla and the mandible FCR: both the maxilla and the mandible were displaced to the right, compared with the frontal midline. Computed tomography scan CT: slight flattening in the high left parietal region
Gilbert-Barness et al. [14]	Multiple meningiomas, craniofacial hyperostosis and retinal abnormalities	Prominence of frontal bone, hypertelorism, proptosis of right eye, and asymmetric overgrowth of mandible in frontal and profile views	Not reported	Not reported

Table 3 (continued)

Author	Main features described	Extraoral examination findings	Intraoral examination findings	Imaging findings
DeLone et al. [15]	Craniofacial and cerebral magnetic resonance imaging features in Proteus syndrome	left hemifacial hypertroph, and left facial palsy	Macroglossia	MRI: large, fibrofatty facial mass with infiltration throughout the left masticator, parotid, and parapharyngeal spaces. The left side of the tongue and masticator muscles were enlarged and diffusely infiltrated with fat. The left mandible, maxilla, zygoma, greater sphenoid wing, and frontal bone were hypertrophied, due primarily to expansion of the marrow space. Hyperostosis of the greater wing of the sphenoid distorted the orbital apex, and there was proptosis secondary to the sphenoid wing, maxillary, zygomatic, and frontal bone expansion
Pinto et al. [16]	Severe mandibular hemihypertrophy and deviation of lower face, in a case of Proteus syndrome previously misdiagnosed as neurofibromatosis	The right hemi- mandibular hyperplasia resulting in prognathism, deviation of the chin point to the left side, and a markedly increased right lower facial height; the right oral commissure was lower than the left; the maxilla showed a slight compensatory asymmetry; mild open bite in the fight buccal segment	Osteoma in the left mandibular alveolus; the lower dental midline deviated to the left	Radiographs (not specified the type of radiographic examination): severe right condylar hyperplasia with a large increase in the vertical height of the ramus and body of the mandible on that side. The posterior facial height was nearly 4 cm greater on the right than on the left. The facial asymmetry was a result of the hemimandibular hypertrophy with no soft tissue, neural, or dental involvement
Arendorf and Hanslo et al. [17]	Enlargement of the gingiva, which was interfering with masticatory function	Macrocephaly, bilateral submandibular lymphadenopathy	Generalized gingival hyperplasia. In the left upper buccal segment, from 23 to 26, the gingival proliferation extended from the buccal to the palatal areas, covering the occlusal surfaces of the involved teeth. All the teeth anticipated at his age were present in the mouth and were normal in size and shape	Not reported
Mason and Roberts [18]	Enamel hypoplasia in Proteus syndrome	Facial and skull asymmetry, exostoses of the nasal bridge and a degree of mandibular prognathism	Reversed incisor overjet and enamel hypoplasia affecting teeth on only one side of the mouth	Not reported

Table 3 (continued)

Author	Main features described	Extraoral examination findings	Intraoral examination findings	Imaging findings
Smeets et al. [19]	Multiple hyperostosis with mandible asymmetry	Multiple hypersostosis (frontal lobe, nasal bridge, right angle of the mandible, right external auditory canal). Asymmetric mandible	Mandibular mucosa with multiple exostosis in the right side; unusual lower frenula; several hypoplastic teeth in the right side of mandible and maxilla	CT: demonstrated the hyperostosis, unilateral condylar hyperplasia

PR panoramic radiograph, *CT* computed tomography, *TMJ* temporomandibular joint, *LCR* lateral cephalometric radiograph, *FCR* frontal cephalometric radiograph

Furthermore, this examination can be useful to detect cervical vertebrae enlargement, although it is not the main examination for the cervical spine [10]. Vertebrae enlargement is present in 19% of PS patients [22].

Moreover, frontal cephalometric radiographs can be useful to confirm the bone asymmetry, [11, 13] and they also allow the verification of cranial exostosis [11]. The cranial and maxillo-mandibular-facial exostosis in PS patients results in disfigurement, which eventually leads to the necessity of surgical approach [9]. These bone lesions may also contain fatty tissue [22].

Computed tomography is useful in the determination of the hyperostosis size and delineation in PS patients, [8–10, 19] as well as bone enlargement [12] to plan for surgical treatment, if needed. Furthermore, computed tomography is performed to verify temporomandibular joint integrity.

The temporomandibular joint may also show degenerative changes, which lead to joint dysfunction in PS patients [8]. The asymmetric overgrowth in PS is often associated with abnormal bone edges from hyperproliferation of osteoid tissue with variable calcification and disorganized bone, as well as abnormally calcified connective tissue and bone invasion of joint spaces, resulting in decreased mobility of the affected joint [5, 22]. Hence, PS patients may suffer from trismus and lateral mandible dislocation with open mouth movements.

Additionally, magnetic resonance imaging findings associated with PS were described in a single case report, which observed, in addition to bone hypertrophy, fibro-adipose mass infiltration in distinct maxillofacial spaces [15]. The dysregulation of adipose tissue is typical in PS and can be observed throughout the entire body [26].

The prognosis of PS mainly depends on the location and the size of the overgrown tissue and the presence of complications [27]. The most frequent complication is deep venous thrombosis and pulmonary embolism [21, 27]. Depending on the severity of anomalies, life expectancy ranges from 9 months to 29 years [24, 28]. PS treatment often includes in addition to dental procedures, vascular surgery, plastic surgery, and pneumology [24, 28]. Skeletal overgrowth may result in facial dysmorphia and functional limitations, which may also demand psychological support.

In conclusion, oral manifestations of PS, which can be detected by plain radiographs commonly requested in dentistry, such as panoramic radiographs, may include dental agenesis, impacted teeth, malocclusion, asymmetric dental growth and maturation, frontal line displacement, and ectopic eruption. Asymmetric tongue enlargement can be noted on clinical examination and magnetic resonance imaging examination. Maxillofacial manifestations may include mandibular hemihypertrophy and asymmetry, presence of exostoses/hyperostosis, degenerative changes in the temporomandibular joint, alterations of maxillary

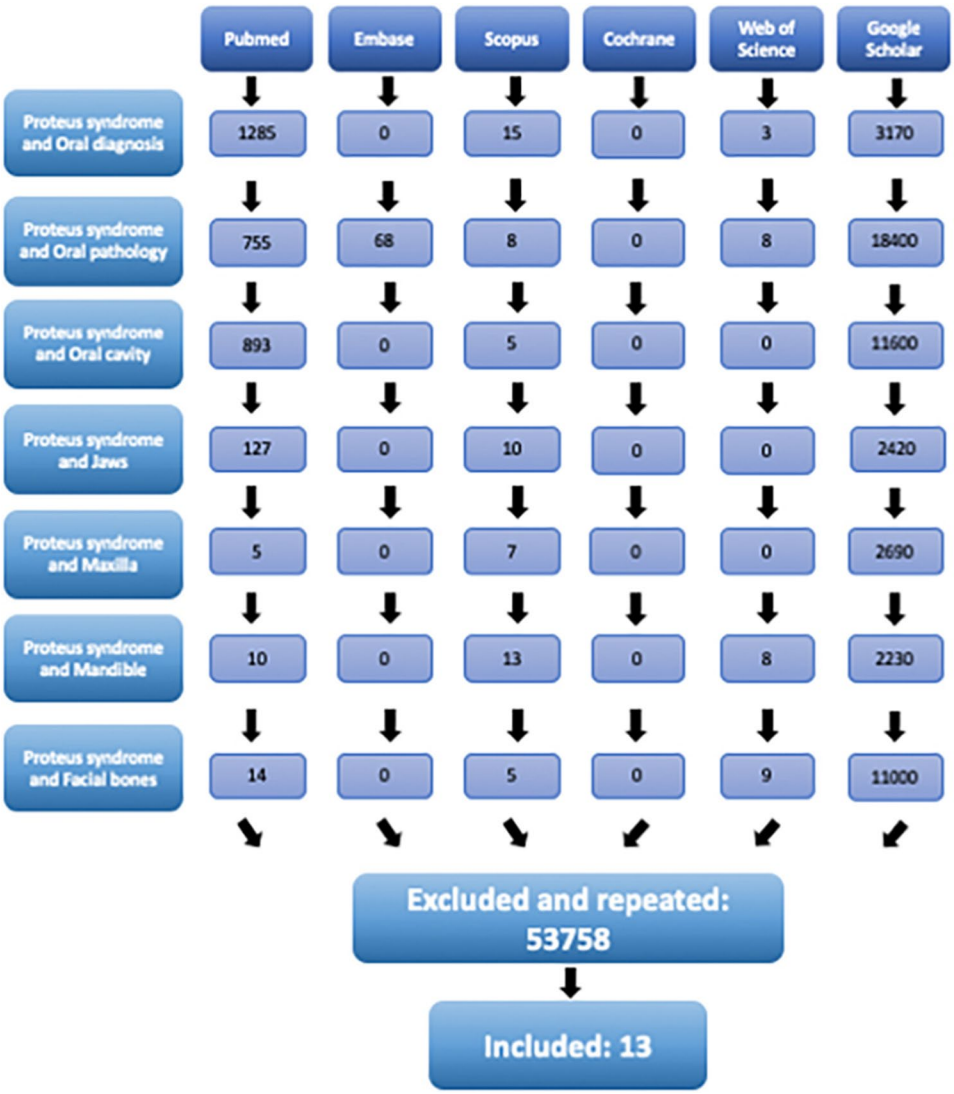

Fig. 5 Extraoral, intraoral, and imaging findings pertaining to oral manifestations of Proteus syndrome

and mandibular vertical and/or horizontal growth, and enlargement of the mandibular canal and foramen.

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Compliance with ethical standards

Conflict of interest Luciana Munhoz, Danielle Ayumi Nishimura, Plauto Christopher Aranha Watanabe, and Emiko Saito Arita declare no conflicts of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. As the product presented in the text is not tested in humans, as specified in the manuscript text, informed consent was not already obtained from all the patients.

Animal rights statements This article does not contain any studies with human or animal subjects performed by any of the authors.

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