RESEARCH

Tumor induced osteomalacia in head and neck region: single center experience and systematic review

Ravikumar Shah[1], Anurag R Lila[1], Swati Ramteke-Jadhav[1], Virendra Patil[1], Abhishek Mahajan[2], Sushil Sonawane[1], Puja Thadani[1], Anil Dcruz[3], Prathamesh Pai[3], Munita Bal[4], Subhada Kane[4], Nalini Shah[1] and **Tushar Bandgar[1]**

[1]Department of Endocrinology, Seth GS Medical College & KEM Hospital, Parel, Mumbai, India
[2]Department of Radiodiagnosis and Imaging, Tata Memorial Hospital, Mumbai, Maharashtra, India
[3]Department of Head Neck Surgery, Tata Memorial Hospital, Mumbai, Maharashtra, India
[4]Department of Pathology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Correspondence should be addressed to A R Lila: anuraglila@gmail.com

Abstract

Tumor-induced osteomalacia in the head and neck region remains a challenging diagnosis to manage. Literature pertaining to management and outcome details remains sparse. We describe two cohorts: cohort 1 included seven patients from a single center in Western India with tumors located in paranasal sinuses (n = 3), intracranial (n = 2) and maxilla (n = 2). The unique features from our series is the management of persistent disease with radiation therapy (n = 2) and peptide receptor radionuclide therapy (PRRT) (n = 1). Cohort two has 163 patients identified from 109 publications for systematic review. Paranasal sinuses, mandible, intracranial disease, maxilla and oral cavity, in descending order, are reportedly common tumor sites. Within this cohort, mean age was 46 ± 14 years at presentation with 44.1% having local symptoms. Duration of symptoms varied from 1 to 240 months. Pre-surgery mean serum phosphorus was 1.4 ± 0.4 mg/dL and median FGF-23 levels were 3.6 (IQR:1.8–6.8) times of normal upper limit of normal. Majority (97.5%) were managed primarily with surgical excision; however, primary radiotherapy (n = 2) and surgery combined with radiotherapy (n = 2) were also reported. Twenty patients had persistent disease while nine patients had recurrence, more commonly noted with intracranial and oral cavity tumors. Surgery was the most common second mode of treatment employed succeeded by radiotherapy. Four patients had metastatic disease. The most common histopathological diagnosis reported is PMT mixed connective tissue, while the newer terminology 'PMT mixed epithelial and connective tissue type' has been described in 15 patients.

Key Words

- tumor-induced osteomalacia (TIO)
- oncogenic osteomalacia
- head and neck
- systematic review

Endocrine Connections (2019) **8**, 1330–1353

Introduction

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare paraneoplastic syndrome caused by overproduction of fibroblast growth factor 23 (FGF23) by a tumor. FGF-23 plays a vital role in renal phosphate handling and vitamin D synthesis. Hence, TIO is characterized by hypophosphatemia due to renal phosphate wasting, inappropriately normal or low 1,25 dihydroxy vitamin D, and elevated or inappropriately normal plasma FGF-23. These biochemical alterations eventually result in osteomalacia. Due to its rarity, the diagnosis of TIO is delayed with the average time from onset of symptoms to diagnosis being more than 2.5 years (1). As a result, patients often present in a debilitated state with multiple fractures, severe muscle weakness

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

and loss of height due to skeletal deformities. Even with a high index of suspicion, tumor localization remains challenging as the offending tumor may be very small and can be anywhere in the body. Complete tumor resection remains the mainstay of treatment and is known to result in dramatic resolution of symptoms.

The first case of TIO was reported by Robert McCance in 1947 who treated a patient having low phosphorus levels and bone pain with high doses of vitamin D suspecting her to be a case of 'vitamin D resistance'; however, the symptoms did not completely resolve until a tumor found in the femur was removed (2). Thereafter, more than 300 cases of TIO have been reported in literature with more than 200 being reported since 2000 (3). The most common tumor site is the lower extremity (>40%) followed by the head and neck region (>20%) (4). There have been several reviews on pathological characters of such tumors but there is no comprehensive review describing clinical characteristics and management of patients with TIO in head and neck region. This article aims to describe a single-center experience with TIO involving the head and neck region followed by a comprehensive clinically oriented review of world literature for the same.

Materials and methods

Cohort 1

Medical records of patients attending Department of Endocrinology, KEM Hospital, Mumbai who were diagnosed with TIO from January 2005 till August 2018 were reviewed after obtaining approval from Institutional Ethical Committee II, Seth G S Medical college and KEM Hospital, Mumbai. Informed consent for the photographs, publication of their clinical details and/or imaging was taken. Patients diagnosed with TIO involving the head and neck region were identified and reviewed for inclusion. Concurrently, patients diagnosed with TIO in other regions, and patients with secondary TIO (3) (including neurofibromatosis, epidermal nevus syndrome, and polyostotic fibrous dysplasia of bone) were excluded from the study.

Diagnosis of TIO was considered in patients presenting with features of hypophosphatemia in absence of relevant family history, evidence of renal phosphate wasting (as demonstrated by low % fractional tubular reabsorption of phosphate (TRP) and tubular maximum for phosphate corrected for glomerular filtration rate (TMP/GFR)) with elevated fibroblast growth factor-23 (FGF-23). Only those patients who had anatomical/functional imaging (CT/MRI or Ga-DOTATATE PET/CT) demonstrating localization of tumor in head and neck region have been included for analysis ($n=7$).

Biochemical parameters recorded pre-operatively include S. calcium, S. phosphorus, S. alkaline phosphatase (ALP), TMP/GFR, TRP and FGF23 levels, and post-operatively include S. phosphorus and FGF-23 levels. Normal ranges for various parameters at our institute are as follows: S. calcium (9–10.5 mg/dL), S. phosphorus (2.5–5 mg/dL), S. ALP (<117 U/L), TMP/GFR (age- and sex-adjusted values as recommended by Chong *et al.* (3)), TRP (>85%) and C-terminal FGF-23 (0–150 RU/mL). Furthermore, details from imaging studies done for localization (CT or Ga-DOTATATE PET/CT), treatment modality used, and histopathology reports have been included for analysis. For patients having recurrent disease additional information including time of recurrence following primary management, biochemical profile, localization of recurrent disease and secondary modality of treatment used was documented.

Tubular resorption of phosphate was measured from phosphate and creatinine levels in a spot fasting urine and serum samples at baseline before starting phosphate supplements. TMP/GFR was calculated with use of a nomogram reported by Bijvoet *et al.* FGF23 was assessed by enzyme-linked immunosorbent assay (FGF23 (C-terminal) kit, Immunotopics, Inc, San Clemente, CA, USA). The kit has sensitivity, an intra-assay coefficient of variation (CV), and an inter-assay CV of 30 RU/mL, 5 and 7.3%, respectively. Serum 1,25(OH)2 vitamin D was assessed by radioimmunoassay (RIA), using a DIA source RIA CT kit by DIA source Immunoassays, SA, with an intra-assay CV of 4.5–9.3% (at 77.3 and 24.5 ng/L concentrations, respectively) and inter-assay CV of 11.3–12.7% (at 33.4 and 13.6 ng/L concentrations, respectively). Whole-body (head to toe) scanning with two acquisitions were obtained 1–1.5 h post intravenous injection of 74–111 MBq of DOTATATE labeled with 68Ga. 68Ga was obtained from an in-house 68Ge/68Ga generator. Scans were acquired on a GE Discovery STE PET/CT with 128 × 128 matrix size and 3 min per bed position of iterative algorithm time. The numbers of bed positions were dependent on the height of the patient, usually 10–12 per patient. CT scans were obtained on a 64-slice Phillips Brilliance CT scanner, while MRI scans were performed on a 1.5 tesla Siemens Sonata (Henkestrabe, Germany) MR scanner.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Cohort 2

We searched for all original and review articles in PubMed till June 2019 (Fig. 1). Individual search was carried out for terms 'Tumour-Induced Osteomalacia', 'Oncogenic Osteomalacia', and 'Phosphaturic Mesenchymal Tumour'. All original and review articles published in English were reviewed for inclusion. Only publications describing TIO in head and neck region were included. A secondary search for relevant publications was carried out by handsearching through the reference lists of selected publications. Hence, in addition to the cases described in our series, we reviewed 163 index cases from 109 publications of TIO of head and neck region previously reported in literature. Clinical profile, biochemical investigations, imaging modality used for localization, location of tumor, treatment modalities used, histopathology findings, recurrence and its management, and metastasis if any were noted. Whenever serum levels of calcium, phosphorus, parathyroid hormone (PTH), 1,25 (OH)2 vitamin D3 levels were available in SI units, they were converted to conventional units with online calculators for uniformity in documentation. Serum ALP when available in units/liter only was included for analysis, while values reported in any other units were excluded due to non-availability of a suitable conversion method.

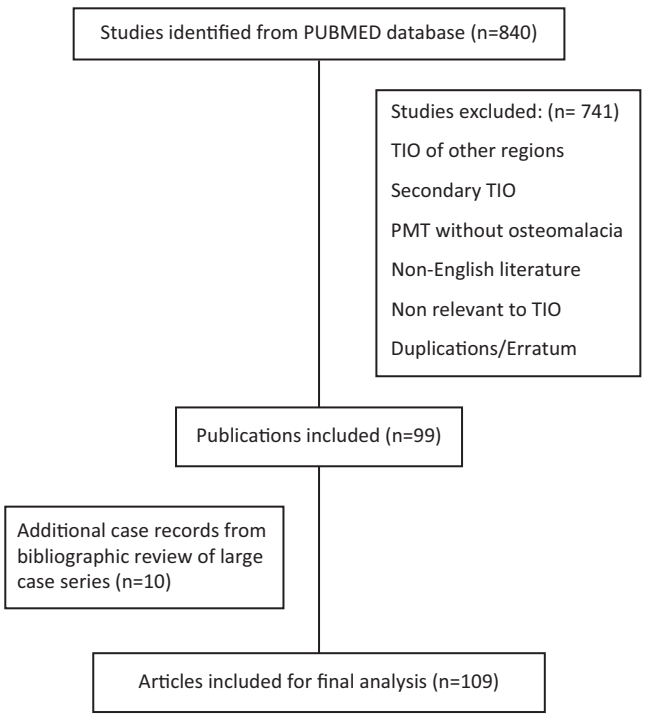

Figure 1
Flowchart of search strategy and selection of studies for inclusion in systematic review.

Statistical analysis

Statistical analysis was performed using SPSS software version 23.0. Mean (±standard deviation (S.D.)) was used for continuous variables when they were normally distributed and median (interquartile range (IQR)) was used for variables with skewed distribution. The difference between categorical variables was analyzed using chi-square test. P value <0.05 is considered significant.

Results

Cohort 1

This cohort includes seven index patients with TIO involving head and neck region. Their characteristics are described in Table 1. The cohort comprised four males and three females with mean age of 42.7±10.6 years whose tumors were located in paranasal sinuses (n=3), maxilla (n=2), and intra-cranially (n=2). All patients presented with bone pain and muscle weakness, while pathologic fractures (n=4) and local symptoms (n=5) were present in majority of patients. The time lag from onset of symptoms to diagnosis was lengthy (mean: 65.1±50.3 months). In four patients, location of tumor was suspected at initial presentation based on clinical history and examination. Thereafter, tumor location was confirmed with Ga-DOTANOC in two patients, with MRI in one patient and CT in one patient. Three patients were primarily detected on Ga-DOTANOC/DOTATATE PET/CT; one patient had a history of epistaxis elicited retrospectively after tumor localization. Mean tumor size was 3.6±1.3 cm. Except for one patient (who was initially operated at another hospital), pre and post-operative serum phosphorus and FGF-23 levels were available in all patients (Table 1). Three patients were cured with initial surgery, while four had persistent disease. No recurrence was documented in patients cured initially (n=3) over a mean follow-up of 17 months. Out of four patients with persistent disease, one patient was cured with repeat surgery only, two patients were cured with repeat surgery and external beam radiation therapy (EBRT), and one has stable disease after peptide receptor radionuclide therapy (PRRT). Histopathologic findings revealed phosphaturic mesenchymal tumor mixed connective tissue type (PMTMCT) in four patients, while the remaining three patients had PMT-OF (ossifying fibroma like), hemangiopericytoma, and odontogenic fibroma, respectively. Clinical images of case numbers one, five and six are shown in Figs 2, 3 and 4 respectively.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 1 Details of cohort 1 patients.

Case no.	Age/sex	Location of tumor	Clinical features			Imaging characteristics		S. Phosphorus (mg/dL)		FGF-23 (RU/mL) (0–150)	
			Local symptoms	Features of TIO	Duration (months)	Localization with	Size of tumor (cm)	Pre-op	Post-op	Pre-op	Post-op
1	32/F	Right maxillary alveolus	Swelling over right alveolus	P, F	84	History and PE	1.2	1.9	4.3	950	102
2	46/M	Left petrous tumor	Earache, protruding mass from left ear	P, MW, F	156	History and PE	5	1.2	3.3	NA	118.6
3	60/M	Left ethmoid sinus	Epistaxis	P, MW, F	12	Ga-DOTANOC	4.7	0.9	1.8	646	72.5
4	39/M	Right frontal & ethmoid sinus	No	P, MW	48	Ga-DOTANOC	2.3	0.9	1.03	787	191
5	53/F	Base of the skull	No	P, MW	36	Ga-DOTATATE	3.5	1.5	NA	725	153
6	33/F	Right maxilla	Right upper gum swelling	P, MW, F	36	History and PE	3	0.6x	1.3	8898	85
7	36/M	Right nasal cavity	Epistaxis, nasal obstruction	P, MW	84	History and PE	5	1.9	4	2024	82

Case no.	Surgical management		Persistence	Second line modality			Total duration of follow-up	Status	Histopathology
	Procedure	Complete resection		Surgery	RT	PRRT			
1	Infrastructure maxillectomy	Yes	–	–	–	–	48	Cured	Odontogenic fibroma
2	Retromastoid craniotomy with left petrosectomy	No	Yes	–	Yes	–	96	Cured	Hemangiopericytoma
3	FESS	No	Yes	FESS 2 times	IMRT 54 Gy in 30 fractions	–	36	Cured	PMTMCT
4	Frontal craniotomy and excision	No	Yes	Endoscopic endonasal tumor excision	–	–	29	Cured	PMTMCT
5	Retromastoid craniotomy with tumor excision	No	Yes	Yes	–	Yes	13	Persistence	PMTMCT
6	Right maxillectomy	Yes	No	–	–	–	12	Cured	PMT OF like
7	Endoscopic endonasal tumor excision	Yes	–	–	–	–	2	Cured	PMTMCT

F, fractures; FESS, functional endoscopic sinus surgery; IMRT, intensity-modulated radiation therapy; MW, muscle weakness; NA, not available; OF, ossifying fibroma like; P, pain; PE, physical examination; PMTMCT, phosphaturic mesenchymal tumor mixed connective tissue type; PRRT, peptide receptor radionuclide therapy; RT, radiation therapy.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

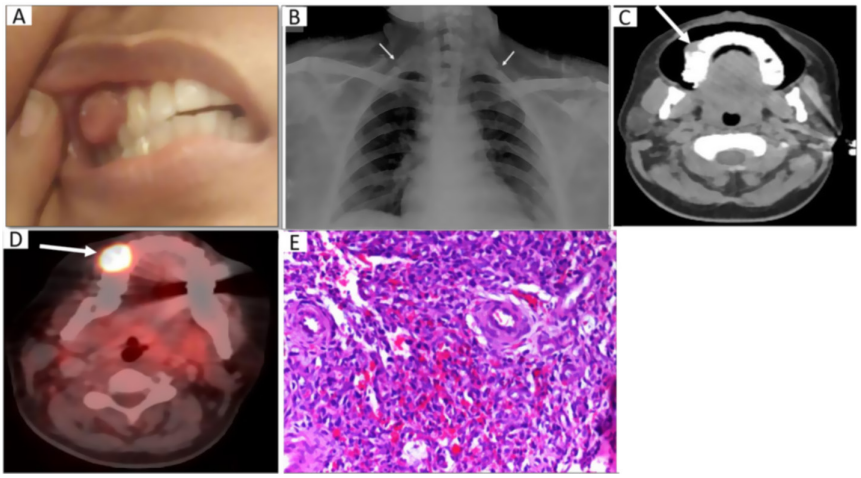

Figure 2
(Case 1): A 32-year-old female presented with bone pains and multiple fractures for 7 years. On examination, approximately 2 cm-sized round swelling in right upper alveolus was seen (A). Preoperative chest radiograph (image contrast adjusted) showing Looser's zone along lateral border of scapula (arrows) suggestive of osteomalacia (B). Axial contrast-enhanced CT image soft tissue window showing small enhancing lesion in right upper alveolus (arrow) extending from canine to 1st molar tooth causing erosion of right upper alveolus (C). Ga-DOTATATE PET scan showing increased uptake at the level of right maxillary alveolus (arrow) (D). After excision histopathological examination showing tumor comprising of spindle cells with scattered osteoclastic giant cells bearing histologic semblance to giant cell granuloma (odontogenic fibroma) (E) (H&E, 400×).

Cohort 2

This cohort consists of 163 index patients from 109 publications. Pertinent data relevant to index patients is provided in Table 2. Details of clinically relevant parameters are summarized in Table 3. Tests done using two different methods have been tabulated separately in Table 3. Due to heterogeneity in reporting of various parameters, the number of cases included (as denominator) have been specified for each parameter. The mean age was 46±14 years with equal male:female ratio. The reported frequency of tumor sites, in descending order, are paranasal sinuses, mandible, intracranial, maxilla, oral cavity and others. Approximately half the patients (44.1%) had evident local symptoms. Bone pain and muscle weakness were most commonly reported. Late complications of hypophosphatemia such as fractures (61%) and bony deformities including kyphosis/scoliosis with resultant height loss (25.7%) were seen in a significant number of patients. Most patients were diagnosed late in their disease course, despite early access to health care, with median duration from symptom onset being almost 4 years. Out of 163 patients, median elevation of FGF-23 up to 3.6 times ULN has been reported in 55 patients with the interquartile range (IQR) being 1.8–6.8×ULN. The primary treatment modality was surgery in most

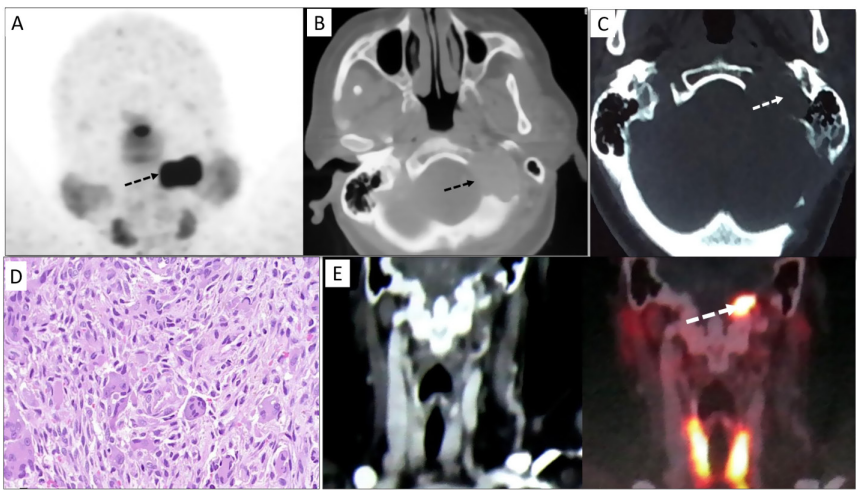

Figure 3
(Case 5): A 53-year-old female presenting with pain in bilateral groins and difficulty in walking for 3-year duration. As investigations confirmed the diagnosis of FGF-23-dependent hypophosphatemic osteomalacia, ^{68}Ga-DOTATATE PET scan was done to locate the tumor which showed increased uptake in base of skull in left side (dashed arrows) (A). Corresponding axial CT images (B) showing soft tissue density lesion involving occipital bone on left side with erosion of the mastoid and petrous part of adjacent temporal bone. Retromastoid craniotomy with tumor excision was done. Histopathological examination showed hypercellular tumor composed of prominent small blood vessels with areas of hemorrhage (H&E, 200×) (D). Post first surgery repeat ^{68}Ga-DOTATATE scan and corresponding CT images showing residual uptake in base of skull in left side (dashed arrows) in the soft tissue density lesion involving occipital bone on left side with erosion of the mastoid and petrous part of adjacent temporal bone (E). After failed second surgery, patient is now having stable disease after two cycles of PRRT.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

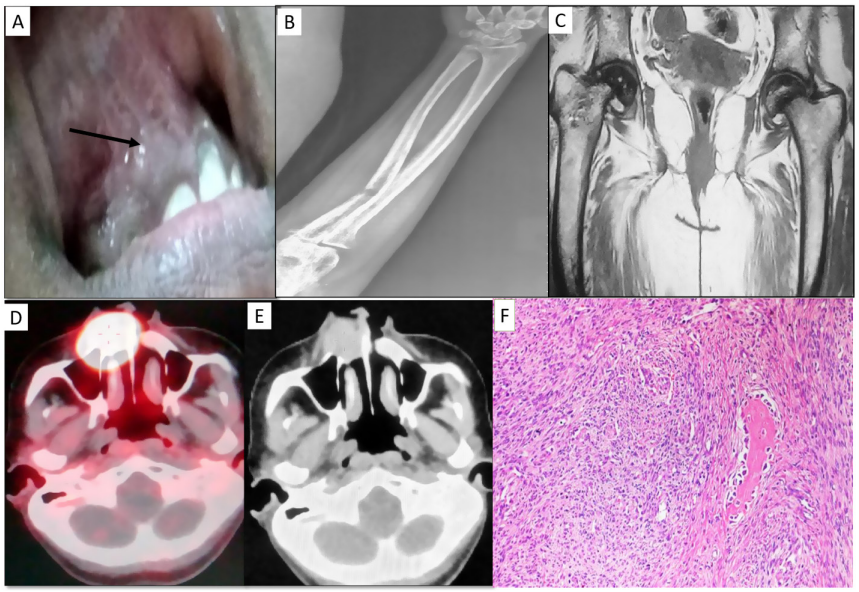

Figure 4
(Case 6): A 33-year-old female presenting with pain in bilateral groins, difficulty in walking and multiple fractures for 3-year duration. There was past history of dental surgery for some 'gum swelling'. On examination, there was swelling in right upper alveolar region (A). X-ray right forearm AP view (image contrast adjusted) showing ulnar shaft fracture (B). MRI hip showing bilateral femoral neck insufficiency fractures which was reported as 'bilateral avascular necrosis' (C). Ga-DOTANOC scan showing uptake in the right maxillary tumor (D). CECT PNS axial view showing 3 cm tumor in right maxillary region (E). Patient was cured with right maxillectomy and osseous reconstruction. Histopathology showed tumor composed of cellular connective tissue intermixed with woven bone displaying osteoblastic rimming (i.e. ossifying fibroma-like histology) (H&E, 100×).

patients (97.5%). Two patients with intracranial tumors, who declined surgery, were treated with primary EBRT. Also, two patients received immediate post-operative EBRT for prevention of recurrence due to fear of incomplete tumor removal.

Out of 148 patients for whom outcome data were available; 119 patients had complete initial response to surgery, 20 patients had persistent disease and 9 patients had recurrence as defined by worsening of post-operatively documented normal biochemistry over a variable period of 2–204 months. Patients with persistent/recurrent disease ($n=29$) were predominantly managed with surgery (65.3%) and/or radiotherapy (30.7%). Among these patients 11 were reported to be alive with no evidence of disease (ANED) and remaining patients were managed with phosphorus supplements with/without other treatment modalities. Four patients had metastatic disease with lymph node and/or lung metastasis. Histopathologically, PMTMCT (48.7%) remains the most commonly reported tumor type followed by hemangiopericytoma (22.7%), PMT of mixed epithelial and connective tissue type (9.4%), giant cell tumor (3.1%) and odontogenic fibroma (3.1%). Other rare types of tumor have been shown in Table 3.

Discussion

TIO is a rare and underreported condition due to unawareness about the characteristic clinical and biochemical profile among treating clinicians. Through this study, we aim to highlight our experience with TIO cases involving head and neck region and provide a review of published literature analyzed on a per-patient basis. This will increase awareness and provide valuable insight on critical management issues for this rare diagnosis.

Cohort 1

A significant time gap between initial presentation till diagnosis persists even in the presence of local symptoms (1). For any atypical head and neck mass, clinician should enquire into history relevant to osteomalacia, and for a symptomatic patient appropriate biochemistry (S. calcium, S. phosphorus and alkaline phosphatase) should be requested. Vice versa, in a patient with non-localized TIO, a clinician should examine oral and nasal cavities for palpable swellings and enquire about relevant local symptoms.

At our center we carry out a complete biochemical evaluation for TIO which includes calcium studies (S. calcium, S. phosphorus, ALP), TMP/GFR, 1,25 (OH) vitamin D3 and FGF-23 levels. FGF-23 serves as a diagnostic marker as well as an indicator of residual disease or recurrence during long-term follow-up. Thereafter, functional imaging with Ga-DOTANOC PET/CT for localization is done. Its superiority compared to FDG-PET/CT is well established (110, 111, 112). Functional imaging is followed by appropriate anatomic imaging to determine tumor extent and plan for surgical management. Alternatively, in a TIO patient presenting with local symptoms or a mass in head and neck region, anatomic imaging (CT/MRI) followed by biopsy can also be used.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 2 Review of published literature on head and neck TIO cases: list of index cases with relevant data.

Case no.	Author	Age/sex	Location of tumor	Duration of symptoms	Localizing imaging	FGF-23		Persistence/ recurrence	Secondary modality	HPR
						Pre-surgery	Post-surgery			
1	Renton (5)	53 F	Left ethmoid	60	X-ray	NA	NA	NA	–	Hemangiopericytoma
2	Sweet (6)	25 F	Left middle turbinate	12	CT	NA	NA	No	–	Hemangiopericytoma
3	Nitzan (7)	26 M	Left mandibular molar legion	24	X-ray	NA	NA	No	–	Giant cell tumor
4	Nomura (8)	29 M	Mandible	24	X-ray	NA	NA	Persistence	RT, chemotherapy, 2nd surgery, chemotherapy	PMT ossifying fibroma like
5	Linsey (9)	54 F	Right nasopharynx	30	CT	NA	NA	NA	–	PMTMCT
6	Shenker (10)	55 M	Neck	NA	NA	NA	NA	No	–	PMTMCT
7	Sheshadri (11)	40 F	Ethmoid sinus	NA	CT	NA	NA	NA	–	Hemangiopericytoma
8	Jefferies (12)	27 F	Left maxillary sinus	24	CT	NA	NA	NA	–	PMT
9	Weidner (13)	39 F	Right maxillary sinus	24	CT	NA	NA	Recurrence	Repeat surgery	Primitive mesenchymal tumor
10	Papotti (10)	38 F	Nasal cavity	NA	NA	NA	NA	No	–	PMTMCT
11	Harvey (10)	32 F	Thyroid	144	PE	NA	NA	Persistence	Repeat surgery: partial f/b total laryngectomy f/b RT and continued on medical management	Malignant PMTMCT
12	Lee (14)	66 F	Left nasal cavity	36	CT	NA	NA	No	–	Hemangiopericytoma
13	Catalano (15)	66 F	Right maxillary and ethmoidal sinus	many years	CT	NA	NA	No	–	Hemangiopericytoma
14	Wilkins (16)	55 M	Left infratemporal mass	24	CT	NA	NA	No	–	Sinonasal hemangiopericytoma like
15	David (17)	60 F	Right subfrontal mass	18	CT	NA	NA	Recurrence	Medical management	Hemangiopericytoma
16	Kim (18)	41 M	Right upper premolar	48	PE	NA	NA	No	–	Giant cell tumor
17	Kim (18)	32 F	Left mandibular molar area	96	PE	NA	NA	No	–	Ossifying fibroma
18	Avila (19)	48 M	Mandible	60	MRI	NA	NA	No	–	Chronic inflammatory tissue with fibrosis and epithelial rests
19	Yang (20)	31 F	Left mandible	96	CT	NA	NA	NA	–	PMT-MCT
20	Gonzalez-Compta (21)	69 F	Right ethmoido-frontal mass	216	CT	NA	NA	Patient died of tumor	–	PMT
21	Ohashi (22)	43 M	Left maxillary sinus	14	CT	NA	NA	NA	–	Hemangiopericytoma
22	Clunie (23)	60 F	Ethmoid sinuses	60	CT	NA	NA	Recurrence	Medical management	Hemangiopericytoma
23	Sandhu (24)	46 M	Right ethmoid sinus	18	CT	NA	NA	No	–	Hemangiopericytoma
24	Reyes-Mugica (25)	9 F	Left mandible	1.5	MRI	NA	NA	No	–	PMT-MCT

(Continued)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 2 Continued

Case no.	Author	Age/sex	Location of tumor	Duration of symptoms	Localizing imaging	FGF-23		Persistence/ recurrence	Secondary modality	HPR
						Pre-surgery	Post-surgery			
26	John (27)	54 F	Right frontal, ethmoidal, sphenoid sinuses	NA	PE	NA	NA	NA	Patient received Immediate RT following surgery	Malignant Schwannoma
27	Reis-Filho (28)	47 F	Cavernous sinus	84	CT	NA	NA	No	–	PMTMCT
28	Fuentealba (29)	63 F	Maxillary sinus	60	CT	NA	NA	Persistence	Surgery, RT, embolization	Hemangiopericytoma
29	Ungari (30)	24 M	Ethmoid	NA	CT	NA	NA	NA	–	Hemangiopericytoma
30	Folpe (10)	29 M	Ethmoid/ sphenoid sinus	24	NA	NA	NA	No	–	Hemangiopericytoma
31	Folpe (10)	46 M	Ethmoid sinus	36	NA	NA	NA	Recurrence	Repeat surgery	Hemangiopericytoma
32	Dupond (31)	71 M	Lower mandible	12	FDG-PET	199 Ru/mL (N <100)	22 Ru/mL (POD 8)	NA	–	PMTMCT
33	Kaylie (32)	46 F	Temporal bone	120	CT	NA	NA	NA	–	PMTMCT
34	Inokuchi (33)	24 F	Right nasal cavity and paranasal sinuses	4	CT	484 Ru/mL (N: 32–84)	58 Ru/mL (POD 3)	No	–	Hemangiopericytoma
35	Yoshioka (34)	45 M	Clivus	10	MRI	NA	49 pg/mL	Recurrence	After first surgery received RT followed by medical management. Octreotide was not effective.	Hemangiopericytoma
36	Koriyama (35)	41 F	Right maxillary sinus	36	CT	309 pg/mL (N: 10–50)	50 (2 h post surgery)	No	–	PMTMCT
37	Elston (36)	69 F	Skull	84	Octreoscan	67 RU/mL (N: 3–45)	32 RU/mL (3–45) (POD 0)	No	–	PMTMCT
38	Beech (37)	42 M	Right ethmoid sinus	84	MRI	NA	NA	No	–	Hemangiopericytoma
39	Ahn (38)	61 M	Left lower buccal vestibule	17	PE	NA	NA	No	–	Hemangiopericytoma
40	Uramoto (39)	48 M	Tongue	24	CT	NA	NA	Recurrence	Second surgery, RT	Malignant PMTMCT
41	Lewiecki (40)	46 M	Mandible	24	Octreoscan	262 RU/mL (N <180)	UD (POD 10)	No	–	PMT
42	Kenealy (41)	79 F	Left ethmoid sinus	NA	CT	355 U/mL (N: 3–45)	NA	NA	–	PMTMCT
43	Kenealy (41)	40 F	Left ethmoid sinus	60	Octreoscan	484 U/mL (N: 3–45)	NA	NA	–	Hemangiopericytoma
44	Kyoung-In Yun (42)	71 F	Mandible	108	PE	NA	NA	No	–	Hemangiopericytoma
45	Woo (43)	42 F	Mandible	108	PE	192 pg/mL (N: 1–71)	98 pg/mL (POD 11)	Persistence	Patient on oral phosphate solution with close follow-up last FGF-23 92 pg/mL	PMTMCT
46	Savage (44)	73 F	Left maxillary sinus	84	111In-pentetreotide	NA	NA	No	–	Hemangiopericytoma

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

47	Kurien (45)	55	M	Right sphenoid, ethmoid sinus	24	CT	NA	NA	No	–	Hemangiopericytoma
48	Gupta (46)	51	M	Nasal cavity	108	FDG-PET	NA	NA	No	–	PMTMCT
49	Gore (47)	52	F	Nasal cavity	48	Octreoscan	573 Ru/mL (N <230)	Normal (45 min post surgery)	No	–	PMTMCT
50	Kobayashi (48)	53	F	Temporal bone	48	SVS	558.8 pg/mL (N: 4–54.3)	Normal (POD 4)	No	–	PMTMCT
51	Shelekhova (49)	70	F	Maxillary sinus	NA	MRI	NA	NA	NA	–	PMTMCT
52	Shelekhova (49)	53	M	Frontal sinus	NA	CT	NA	NA	NA	–	PMTMCT
53	Pedrazzoli (50)	37	F	Right maxillary sinus	32	CT	NA	NA	No	–	Hemangiopericytoma
54	Mori (51)	42	M	Left maxillary alveolus	36	MRI	241 pg/mL (N: 10–50)	Normal (1 h post surgery)	No	–	PMTMCT
55	Parshwanath (52)	42	F	Left nasal cavity and ethmoid sinus	42	CT	NA	NA	No	–	PMT
56	Battoo (53)	34	F	Left nasal cavity	60	PE	NA	NA	NA	–	Giant cell tumor
57	Peterson (54)	33	F	Maxillary sinus	NA	NA	NA	NA	NA	–	PMT
58	Peters (55)	22	M	Right temporal lobe mass	96	PE	NA	NA	Persistence	Three craniotomies with angioembolization, RT, PRRT, octreotide, dasatinib	Hemangiopericytoma
59	Akhter (56)	52	M	C5 vertebrae	NA	FDG-PET	NA	NA	No	–	PMTMCT
60	Xian-Ling (57)	43	F	Right petrous apex	48	MRI	NA	NA	Persistence	Octreotide therapy	PMTMCT
61	Xian-Ling (57)	42	F	Left ethmoid sinus	24	Octreoscan	NA	NA	No	–	PMTMCT
62	Guglielmi (58)	22	M	Left ethmoid sinus	24	Octreoscan	NA	NA	Persistence	Repeat surgery	Hemangiopericytoma
63	Uno (59)	53	F	Right temporal bone	48	CT	>200 (N: 10–50 pg/mL)	<50 (POD-2)	NA	–	PMT-MCT
64	Uno (59)	61	M	Left basi frontalis	60	CT	400 (N: 10–50 pg/mL)	<3 pg/mL (immediately)	Persistence	Repeat surgery	PMT-MCT
65	Andreupoulou (60)	63	M	Left frontal lobe	NA	SVS	156 pg/mL	101 pg/mL (6 months post RT)	At 6 months, patient had declining FGF-23	–	PMTMCT
66	Bergwitz (61)	56	M	Mandible	228	PE	870 Ru/ml (N <180)	NA	Persistence	Multiple surgeries, cinacalcet	Ameloblastic fibrosarcoma
67	Monappa (62)	35	M	Right mandible	36	PE	NA	NA	No	–	PMTMCT
68	Chokyu (63)	57	M	Middle cranial fossa	24	MRI	84 pg/mL (N: 10–50)	14 pg/mL (POD 7)	No	–	PMT
69	Chiam (64)	55	M	Right nasal cavity	18	MRI	232 RU/mL (N <180)	18RU/mL (<180) day 5	No	–	PMTMCT
70	Cho (65)	47	F	Nasal cavity, ethmoidal sinus	36	CT	NA	NA	No	–	Hemangiopericytoma

(Continued)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 2 Continued

Case no.	Author	Age/sex		Location of tumor	Duration of symptoms	Localizing imaging	FGF-23		Persistence/ recurrence	Secondary modality	HPR
							Pre-surgery	Post-surgery			
72	Brandwein-Gensler (67)	66	F	Nasal cavity, maxilla	NA	PE	NA	NA	No	–	Glomangiopericytoma
73	Munoz (68)	60	M	Posterior neck	24	FDG-PET	575 RU/mL (N <180)	Normal	No	–	PMTMCT
74	Chang (69)	37	m	Left nasal cavity	60	PE	NA	NA	No	–	Hemangiopericytoma
75	Jiang (70)	38	F	Mandible	24	Octreoscan	NA	NA	No	–	PMT-MCT
76	Jiang (70)	69	F	Mandible	240	Octreoscan	393 pg/mL (N: 10–50)	8	No	–	PMT-MCT
77	Jiang (70)	28	M	Mandible	48	Octreoscan	NA	NA	No	–	Odontogenic fibroma
78	Jiang (70)	56	F	Mandible	120	Octreoscan	NA	NA	No	–	PMT-MCT
79	Jiang (70)	55	F	Lower gingiva	204	Octreoscan	NA	NA	No	–	PMT-MCT
80	Jiang (70)	45	F	Mandible	132	Octreoscan	NA	NA	No	–	Odontogenic fibroma
81	Jiang (70)	50	F	Mandible	36	Octreoscan	NA	NA	No	–	PMT-MCT
82	Jiang (70)	27	M	Maxilla	72	Octreoscan	NA	NA	No	–	Odontogenic fibroma
83	Jiang (70)	49	F	Nasal sinus	72	Octreoscan	NA	NA	Recurrence	Observation	PMT-MCT
84	Jiang (70)	24	M	Nasal sinus	48	Octreoscan	NA	NA	No	–	PMT-MCT
85	Jiang (70)	45	F	Nasal sinus	120	Octreoscan	NA	NA	No	–	PMT-MCT
86	Jiang (70)	57	F	Nasal sinus	102	Octreoscan	NA	NA	No	–	PMT-MCT
87	Fatani (71)	58	M	Floor of mouth, mandible	240	CT	NA	NA	Recurrence	Multiple surgeries, wedge lung resection	Malignant PMTMCT
88	Mathis (72)	28	F	Cribriform plate	36	MRI	NA	NA	No	–	PMTMCT
89	Mathis (72)	32	M	Anterior cranial fossa, ethmoid sinus	12	CT	NA	NA	Persistence	Multiple surgeries	PMTMCT
90	Tarasova (73)	60	F	Left frontal mass	48	SVS	132 pg/mL (N: 10–50)	134 Ru/mL (N <180) (3 years after RT)	No	–	NA
91	Papierska (74)	40	NA	Right maxillary sinus	NA	Octreoscan	260.4 Ru/ml (N: 5-105)	NA	NA	–	Glomangiopericytoma
92	Lee (75)	60	F	Right maxillary sinus	72	CT	NA	NA	No	–	Glomangiopericytoma
93	Allevi (76)		F	Right maxillary sinus		Octreoscan	NA	NA	No	–	PMT hemangiopericytoma
94	Annamalai (77)	49	M	Left nasal cavity	180	FDG-PET/DOTA	224.5 RU/mL (N <150)	64.6 RU/mL (POD 2)	No	–	PMTMCT
95	Okamiya (78)	35	F	Left ethmoid sinus	8	FDG-PET	147 pg/mL (N: 14–40)	16 pg/mL	No	–	PMTMCT
96	Arnaoutakis (54)	50	F	Right ethmoid sinus	6	PE	NA	NA	NA	–	PMT
97	Mok (79)	48	M	Right maxillary sinus	12	MRI	NA	NA	No	–	PMT
98	Fernández-Cooke (80)	3	M	Maxilla and mandible	6	PE	395.1 pg/mL (N <40) 1267.2 RU/ML (N <60)	Normal	Persistence	RFA, Local steroid infiltration, calcitonin, bisphosphonates, propranolol, cinacalcet	Central giant cell granuloma
99	Fathalla (81)	49	F	Right frontal lobe	36	Octreoscan	609 RU/mL (N: 0–180)	NA	No	–	PMTMCT

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

100	Ray (82)	35	M	Left nasal cavity	24	CT	5 X N	NA	No	–	Hemangiopericytoma
101	Qari (83)	60	M	Gingiva of mandibular teeth	72	PE	NA	NA	No	–	PMT
102	Wasserman (84)	50	M	C3 vertebrae	24	NA	NA	NA	No	–	PMTMCT
103	Wasserman (84)	33	F	Nose, lips, tongue	120	NA	NA	NA	Persistence	NA	Malignant PMTMCT
104	Mani (85)	56	M	Occipital bone	36	PE	NA	NA	No	–	PMTMCT
105	Yu (86)	37	M	Maxilla	36	PE	129.97 pg/mL (N: 33.9–51.6)	64.9 pg/mL	No	–	PMTMCT
106	Yu (86)	50	M	Mandible	6	PE	312.84 pg/mL (N: 33.9–51.6)	NA	No	–	Spindle cell tumor with PMT features
107	Yu (86)	50	M	Left nasal cavity	72	Octreoscan	272.71 pg/mL (N: 33.9–51.6)	5.93 pg/mL	No	–	PMTMCT
108	Yu (86)	38	F	Left nasal cavity and ethmoid sinus	12	Octreoscan	350.9 pg/mL (N: 33.9–51.6)	NA	No	–	PMTMCT
109	Takashi (87)	77	M	Left parotid gland	96	FDG-PET	186.9 pg/mL	6.5 pg/mL	No	–	PMTMCT
110	Gresham (88)	42	M	Ethmoid mass	36	MRI	NA	NA	No	–	Glomangioma
111	Agaimy (89)	48	M	Nasal cavity		NA	NA	NA	NA	–	Cellular, nondescript
112	Lee (90)	33	M	Right mandible	156	Ga-DOTANOC	86.7 pg/mL (N: 10–50)	NA	No	–	Giant cell granuloma
113	Lee (90)	52	M	Left ethmoid sinus	6	Ga-DOTANOC	492.3 pg/mL (N: 10–50)	NA	Persistence	RT	PMT
114	Schober (91)	59	F	Right fronto-basal region	22	SVS	1600 Ru/mL (N: 26–110)	74 Ru/mL	Recurrence	Repeat surgery	Meningioma
115	Zuo (92)	NA	M	Left nasal cavity	36	Octreoscan	NA	NA	No	–	PMT
116	Zuo (92)	NA	F	Left maxillary bone	36	FDG-PET	NA	NA	No	–	PMT
117	Hana (93)	38	M	Bilateral ethmoid sinus	84	MRI	120 pg/mL (N: 10–50)	ND (POD-1)	Persistence	Repeat surgery	PMTMCT
118	Chanukya (94)	31	M	Left nasal cavity	24	Ga-DOTANOC	1310 Ru/mL (N: 0–150)	109 Ru/mL (1 month post surgery)	No	–	Hemangiopericytoma
119	Gonzalez (95)	42	M	Nasofrontal sinus	72	PE	75.9 pg/mL (N: 8–54)	8.4 pg/mL	No	–	PMTMCT
120	Singh (96)	67	M	Posterior wall of mastoid antrum	204	Ga-DOTANOC	237 Ru/mL (N: 0–150)	NA	NA	–	PMT
121	Singh (96)	45	M	Left side of body of mandible	12	Ga-DOTANOC	1553 Ru/mL (N: 0–150)	NA	NA	–	PMT
122	Pelletier (97)	37	M	Mandible	NA	SVS f/b MRI	310 Ru/mL (N: 19–114)	NA	NA	–	NA
123	Pelletier (97)	49	F	Mandible		Octreoscan of growing lesion on MRI with FDG-avidity and gradient on SVS	1194 Ru/mL (N: 19–114)	200 Ru/mL	Persistence	NA	NA

(Continued)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 2 Continued

Case no.	Author	Age/sex	Location of tumor	Duration of symptoms	Localizing imaging	FGF-23		Persistence/ recurrence	Secondary modality	HPR
						Pre-surgery	Post-surgery			
125	Villepelet (99)	41 F	Right ethmoid sinus	NA	CT	NA	48 pg/mL (POD-5)	No	–	PMT
126	Pelo (100)	62 F	Left TMJ	60	PE	NA	NA	No	–	PMT
127	He (101)	54 F	Right parotid	24	Ga-DOTANOC	NA	NA	NA	–	Salivary basal cell adenoma
128	Wu (102)	49 F	Right mandible	216	NA	NA	NA	Persistence	Multiple surgeries	Odontogenic fibroma
129	Wu (102)	20 F	Left maxilla	48	NA	NA	NA	No	–	Odontogenic fibroma
130	Wu (102)	30 F	Right maxilla	60	NA	NA	NA	No	–	PMT of mixed epithelial & connective tissue type
131	Wu (102)	36 M	Left mandible	60	NA	NA	NA	No	–	PMT of mixed epithelial & connective tissue type
132	Wu (102)	25 M	Right maxilla	72	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
133	Wu (102)	15 F	Right mandible	24	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
134	Wu (102)	41 M	Right mandible	60	NA	NA	NA	NA	–	PMT of mixed epithelial and connective tissue type
135	Wu (102)	34 M	Left maxilla	72	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
136	Wu (102)	50 M	Right mandible	18	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
137	Wu (102)	66 M	Right maxilla	108	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
138	Wu (102)	26 M	Left maxilla	36	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
139	Wu (102)	32 M	Right maxilla	36	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
140	Wu (102)	41 M	Right mandible	60	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
141	Wu (102)	22 M	Right mandible	24	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
142	Wu (102)	31 M	Right maxilla	36	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

143	Wu (102)	51	M	Left mandible	132	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
144	Wu (102)	75	M	Right mandible	72	NA	NA	NA	No	–	PMT of mixed epithelial and connective tissue type
145	Ding (103)	66	F	Right nasal cavity	48	Ga-DOTATATE	NA	NA	NA	–	NA
146	Ding (103)	41	M	Right mandible	108	Ga-DOTATATE	NA	NA	NA	–	NA
147	Mishra (104)	46	M	Right temporal lobe mass	60	Ga-DOTANOC	1028 Ru/mL (N <180)	NA	NA	–	PMTMCT
148	Mishra (104)	52	F	Left skull base tumor	24	Ga-DOTANOC	725 Ru/mL (N <180)	150 Ru/mL (3 months post-surgery)	No	–	PMTMCT
149	Li (105)	40	F	Left nasal cavity	12	History	NA	NA	Recurrence	Repeat surgery twice	Hemangiopericytoma
150	Acharya (106)	42	M	Right mandible	12	FDG-PET	332 Ru/mL (N <180)	53 Ru/mL (POD 54)	No	–	PMTMCT
151	Kurien (107)	39	F	Right nasal cavity	24	NA	260 Ru/mL (N <180)	40 Ru/mL	No	–	PMTMCT
152	Kurien (107)	36	F	Left ethmoid sinus	24	NA	NA	126 Ru/mL	No	–	PMTMCT
153	Kurien (107)	51	M	Middle turbinate	36	NA	604 Ru/mL (N <180)	<5 Ru/mL	No	–	PMTMCT
154	Kurien (107)	44	M	Middle turbinate	48	NA	145 Ru/mL (N <180)	94.7 Ru/mL	No	–	PMTMCT
155	Kurien (107)	55	M	Posterior ethmoid, sphenoid	24	NA	NA	NA	No	–	PMTMCT
156	Kurien (107)	37	F	Anterior ethmoid with intracranial extension	36	NA	695 Ru/mL (N <180)	38 Ru/mL	Persistence	RT	Malignant PMTMCT
157	Kurien (107)	62	F	Nasal cavity, all PNS	48	NA	NA	899 Ru/mL	Persistence	Observation	PMTMCT
158	Paul (108)	54	F	Left mandible	24	Ga-DOTATATE	1094 Ru/mL (N <180)	369 Ru/mL (POD-5) 44 Ru/mL (4 months post-surgery)	No	–	PMTMCT
159	Pal (109)	28	M	Mandible	NA	Ga-DOTATATE	201 Ru/mL (N <180)	307 Ru/mL	Persistent	Medical management	Hemangiopericytoma
160	Pal (109)	52	F	Right nasal cavity	NA	Ga-DOTATATE	814 Ru/mL (N <180)	NA	No	–	Arteriovenous hemangioma
161	Pal (109)	36	F	Left maxillary sinus	NA	Ga-DOTATATE	1239 Ru/mL (N <180)	NA	No	–	PMTMCT
162	Pal (109)	58	M	Left nasal cavity	NA	Ga-DOTATATE	513 Ru/mL (N <180)	NA	No	–	Hemangiopericytoma
163	Pal (109)	36	F	Left nasal cavity	NA	FDG-PET	2467 Ru/mL (N <180)	NA	No	–	Hemangiopericytoma

F, female; M, male; N, normal value; NA, not available; OF, ossifying fibroma like; PE, physical examination; PMTMCT, phosphaturic mesenchymal tumor mixed connective tissue type; POD, post-op day; PRRT, peptide receptor radionuclide therapy; RT, radiation therapy; SVS, selective venous sampling of FGF-23; UD, undetectable.

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 3 Summary of literature review.

Parameter	Value	No. of patients with available data
Age (years) (mean ± S.D.)	46 ± 14	160
Sex	81:81	162
Location of tumor % (no.)		163
Paranasal sinuses	43.7 (76)	
Mandible	21.5 (34)	
Intracranial	11.8 (19)	
Maxilla	9 (13)	
Oral cavity	6.2 (10)	
Skull	1.2 (2)	
Parotid	1.3 (2)	
Posterior neck	1.3 (2)	
Cervical vertebra	1.3 (2)	
Infratemporal fossa	0.7 (1)	
Mastoid antrum	0.7 (1)	
Thyroid	0.7 (1)	
Local symptoms % (no.)	44.1 (49)	111
Hypophosphatemic symptoms		
Muscle weakness % (no.)	77.9 (106)	136
Fractures % (no.)	61.2 (68)	111
Bone pains % (no.)	100 (142)	142
Bony deformities % (no.)	25.7 (27)	105
Duration of symptoms (months), median (IQR)	36 (24–72)	139
Biochemical profile		
S. Calcium (mg %) (mean ± S.D.)	8.9 ± 0.5	87
S. Phosphorus (mg %) (mean ± S.D.)		
Pre-op	1.4 ± 0.4	119
Post-op	3 ± 0.7	62
S. Alkaline phosphatase (U/L) (median (IQR))	313 (200–420)	95
TMP/GFR (median (IQR))	0.9 (0.6–1.3)	39
TRP (median (IQR))	61 (46.2–72.2)	21
PTH (pg/mL) (median (IQR))	55.9 (39.3–83.7)	73
1,25 (OH)2 vitamin D3 (pg/mL) (median (IQR))	18 (8.2–26.2)	46
FGF-23 (Pre-op) (median (IQR))		
X ULN	3.6 (1.8–6.8)	55
C-terminal (Ru/mL)	573 (234–1058)	33
Intact (pg/mL)	256 (131–393)	22
FGF-23 (Post-op)		
C-terminal (Ru/mL)	69.3 (36.5–138)	18
Intact (pg/mL)	14 (5.9–50)	15
Tumor size (cm) (median (IQR))	2.5 (1.8–3.2)	70
Localization imaging % (no.)		131
History and PE	16.7 (22)	
X-ray	2.3 (3)	
CT scan	25.9 (34)	
MRI	10.6 (14)	
Octreotide scintigraphy	20.6 (27)	
FDG-PET/CT	8.4 (11)	
Ga-DOTA-based PET/CT	11.4 (15)	
Selective venous sampling of FGF-23	3.8 (5)	
Primary modality of treatment % (no.)		160
Surgery	97.5 (156)	
Radiation therapy	1.2 (2)	
Combined surgery + radiation therapy	1.2 (2)	
Complete response to primary treatment % (no.)	80.4 (119)	148
Persistent disease % (no.)	13.5 (20)	148
Follow-up (months)	13 (5.2–36)	108
Recurrence % (no.)	7 (9)	128
Time to recurrence (months) (range)	2–204	

(Continued)

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Table 3 Continued

Parameter	Value	No. of patients with available data
Site wise persistence/recurrence % (no./no.)		
Paranasal sinuses	14.4 (7/4)	76
Mandible	17.6 (6/0)	34
Intracranial	36.8 (4/3)	19
Maxilla	7.6 (1/0)	13
Oral cavity	33.3 (1/2)	10
Thyroid	100 (1)	1
Secondary modality of treatment % (no.)		26
Surgery	65.4 (17)	
RT	30.8 (8)	
Chemotherapy	7.7 (2)	
Cinacalcet	7.7 (2)	
Octreotide	7.7 (2)	
Radiofrequency ablation	3.8 (1)	
PRRT	3.8 (1)	
Others	3.8 (1)	
Metastasis % (no.)	2.7 (4)	148
Histopathology % (no.)		158
PMTMCT	48.7 (77)	
PMT ossifying fibroma like	1.3 (2)	
PMT mixed epithelial and connective tissue type	9.5 (15)	
Malignant PMTMCT	3.2 (5)	
Hemangiopericytoma	22.8 (36)	
Giant cell tumor	3.2 (5)	
Odontogenic fibroma	3.2 (5)	
Glomangiopericytoma	2.5 (4)	
Malignant schwannoma	0.6 (1)	
Meningioma	0.6 (1)	
Salivary basal cell adenoma	0.6 (1)	
Ameloblastic fibrosarcoma	0.6 (1)	
Primitive mesenchymal tumor	0.6 (1)	
Arteriovenous hemangioma	0.6 (1)	
Spindle cell tumor with PMT features	0.6 (1)	
Cellular non-descript	0.6 (1)	
Chronic inflammatory tissue with fibrosis and epithelial cell rests	0.6 (1)	

Complete surgical removal with wide margin of excision remains the cornerstone of management in these cases (3). This is particularly difficult in intracranial tumors resulting in persistent disease as noted in both our patients with intracranial tumors.

S. Phosphorus and FGF-23 levels are used for post-operative surveillance. Half-life of FGF-23 is very short and one can document it immediately post-operatively (93). Persistent elevation of FGF-23 was noted post-operatively in two patients (cases 1 and 6), which normalized on re-evaluation after 3 months. This observation has been previously reported particularly with C-terminal FGF-23 assay (108, 109). Phosphate supplements are discontinued post-operatively to allow for surveillance. Reimaging is performed in patients with persistent symptoms and biochemically active disease.

In recurrent or persistent cases, complete tumor removal resulted in cure in two patients, hence, this remains the preferred approach at our institute. In inoperable cases, two patients received external beam radiotherapy (EBRT) and one patient received peptide receptor radiotherapy (PRRT). In one patient (Case 2) EBRT was given after first surgery due to difficult tumor location at petrous apex. He had a gradual and complete response to RT over next 4 years. In another scenario (case 3), the patient had persistent disease after functional endoscopic sinus surgery (FESS) for left ethmoid sinus tumor. Following two repeat FESS, patient was considered for EBRT for persistent disease. Patient received IMRT 54 Gy in 30 fractions. S. Phosphorus and FGF-23 normalized gradually over one and half years and this patient who was previously bedbound is now walking without any support.

One patient (case 5) in our cohort has received PRRT for persistent disease after two surgeries for base of skull tumor (113). As tumor was Ga-DOTATATE avid having

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

Krenning score IV, patient was considered for PRRT after a thorough discussion in a multidisciplinary meeting. This patient has stable disease after two cycles of PRRT with 150–200 uCi ^{177}Lu-DOTATATE.

PMTMCT remains the commonest histopathologic entity in these patients. We also reported one patient for each of the following: PMT-OF like, odontogenic fibroma and hemangiopericytoma in our cohort. Detailed histopathological findings for cases three, four and six have been published previously (114).

Although the sample size of cohort 1 was small, the epidemiological data are similar to cohort 2. There is an increased prevalence of local symptoms at presentation and higher rate of persistence following primary surgery at our center. This could be attributed to referral bias to a tertiary care center.

Cohort 2

Here we present a detailed review of published English literature for TIO cases involving head and neck region (n=163) (5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109). This is the largest series of its kind published to date.

Epidemiology

As is the case with overall TIO literature, almost equal male:female ratio is reported in head and neck TIO patients (3). Middle age is the most common age at presentation and three pediatric cases are reported so far. TIO is a difficult diagnosis in pediatric patients as heritable hypophosphatemic rickets is a more likely diagnosis unless the tumor is evident. Fernández-Cooke *et al.* have reported a 3-year-old child with rickets and a jaw tumor. Two years went by before a link was established between the two and a diagnosis of TIO was made (80). In the case described by Reyes-Mugica *et al.* the heightened awareness of pediatric endocrinologist for this condition led to early screening with imaging and subsequent surgical removal resulting in cure within 6 weeks of onset of symptoms (25). In the third case reported by Wu *et al.* also the duration of hypophosphatemic symptoms was 2 years (102).

The time from symptom onset to final diagnosis remains dreadfully long. In this series of cases of TIO involving head and neck region, only 10% (n=14) were diagnosed in the first year of disease onset with majority of them having local symptoms at presentation. Feng *et al.* observed a misdiagnosis rate of 95.1% with 240 case-times of misdiagnoses among 144 cases of TIO even in the presence of evident hypophosphatemia in 43.1% cases (115). Reasons cited for misdiagnosis were disease rarity, insidious onset, nonspecific clinical manifestations and poor recognition by the clinician. Presence of local compressive symptoms and/or swelling in approximately 50% patients in this review highlights the problem of delayed or missed diagnosis as musculoskeletal symptoms are ignored until presentation with advanced local symptoms.

Biochemical profile

The typical biochemical profile in TIO is straightforward: hypophosphatemia with normocalcemia, moderately elevated ALP, normal PTH, inappropriately normal-to-high urinary phosphate excretion, low serum 1,25 (OH)2 vitamin D3 and elevated FGF-23 levels (3).

FGF-23 is useful as a tumor marker. Based on two case reports, half-life of FGF-23 is between 20–50 min (116, 117). More recently, Hana *et al.* reported half-life of FGF-23 to be 18.5 min in a patient with intracranial PMTMCT using intact FGF-23 assay (93). This allows FGF-23 to be used for intraoperative monitoring to determine the extent of tumor removal. Immediate post-op decline in FGF-23 levels within normal range is reported by other investigators (36, 47, 51, 59) as well. Elston *et al.* reported discordant increase in C-terminal FGF-23 post-op which has not been confirmed by other studies (36). As previously stated, persistent elevation in C-terminal FGF-23 in immediate post-operative period has been documented despite complete tumor removal (108, 109). With no reports on levels of other postulated phosphotonins like matrix extracellular phosphoglycoprotein (MEPE) and secreted frizzled-related protein 4 (SFRP4) in patients with TIO, their role still remains unclear (118).

Location of tumor

Most common site for TIO in head and neck region is paranasal sinuses. Among them, ethmoid sinuses are the most common site followed by maxillary, sphenoid and frontal sinuses. Most common tumors are PMTMCT, hemangiopericytoma and glomangiopericytoma, in descending order. The second most common site is bony tumors arising from the mandible and maxilla with

odontogenic fibroma and, PMT of mixed connective tissue and epithelial components as special tumor types. Third position is for intracranial tumors involving anterior cranial fossa, middle cranial fossa, and posterior cranial fossa, in descending order of prevalence. Reported tumors include PMTMCT, hemangiopericytoma and meningioma. Tumors of oral cavity include gingival tumors (molar/premolar), tongue and buccal vestibule in that order of occurrence. Apart from PMTMCT (including malignant) and hemangiopericytoma, tumors from this region also include giant cell tumor and ossifying fibroma. Rarely tumors have been reported from skull, parotid glands, posterior neck, infratemporal fossa, mastoid antrum, thyroid and vertebra.

Localization imaging

Classically, history of local compressive symptoms and/or visible mass on physical examination is instrumental in diagnosing TIO even in this current era of sensitive imaging modalities. Earlier clinicians were dependent on physical examination and x-rays for diagnosing TIO. Renton *et al.*, Nitzan *et al.*, and Nomura *et al.* have localized head and neck TIO through x-rays alone (5, 7, 8). With the introduction of CT scans (1980–2000), 60% tumors in the head and neck region were localized with this modality. The first localization of head and neck TIO on MRI was reported by Avila *et al.* in 1996 using MR skeletal survey (19).

Following *in vitro* demonstration of somatostatin receptors (SSTRs) by Reubi *et al.* (119), scintigraphic studies using ^{111}In-pentetreotide for tumor localization was published by De Beur *et al.* in 2002 (120). Subsequently, localization with ^{99}mTc-MIBI and FDG-PET scans was reported (121, 122). Use of FDG-PET was limited due to poor specificity of non-receptor-based imaging, and slow-growing nature of these tumors resulting in false-negative results (96). With improved spatial resolution, lower radiation dose and more rapid whole-body tomographic imaging of PET/CT studies in comparison to scintigraphy, ^{68}Ga-DOTA-based PET/CT scans became the investigation modality of choice in TIO patients (112, 123). Various studies have shown superiority of ^{68}Ga-DOTATATE PET/CT and ^{68}Ga-DOTANOC PET/CT over FDG-PET/CT and Octreoscan for tumor localization in TIO (110, 111, 112). The largest such study is that of 54 patients by Zhang *et al.* using ^{68}Ga-DOTATATE PET/CT reported 100% sensitivity and 90.9% specificity in lesion detection (124). Use of positron emitter radiotracer ^{68}Ga enabling PET-based imaging along with higher affinity SSTR ligands like DOTATATE (SSTR 2>5) and DOTANOC (SSTR 2,3,5) are postulated to be responsible for enhanced sensitivity of ^{68}Ga-DOTA-based PET/CT over Octreoscan (112). Thereafter, Singh *et al.* highlighted the issue of multiple low-grade benign uptakes using ^{68}Ga-DOTANOC PET/CT especially at fracture sites and described the use of SUVmax and anatomical imaging showing soft tissue component in the lesion to pinpoint the causal lesion (96). In summary, Ga-DOTA-based PET/CT is superior to other functional studies like FDG-PET and Octreoscan, but its utilization will depend on local availability and expertise (119).

Selective venous sampling of FGF-23 has been studied for accurate localization of TIO. Kobayashi *et al.* used selective venous sampling as an initial guiding modality localizing the tumor to right head and neck region, although on retrospect distortion of right external ear canal was noted and no prior functional imaging was done to localize the tumor (48). Andreopoulou *et al.* reported sensitivity of 87% and specificity of 71% at FGF-23 concentration ratio of 1.6 between the venous drainage of the tumor bed and general circulation after sampling 17 major veins and their branches (60). They concluded that selective venous sampling is not useful in the absence of suspicious lesion on imaging studies and its use should be limited to cases with multiple suspicious sites or before resection in anatomically challenging cases. In 2017, Lee *et al.* reported contrasting results. In their cohort, five patients negative on both ^{111}Indium-octreotide scintigraphy and FDG-PET/CT were subjected to selective blood sampling from 10 to 14 sites (90). They identified the culprit lesion on follow-up with targeted MRI or whole-body Ga-DOTATOC in four patients. Tarasova *et al.* and Shober *et al.* have used selective venous FGF-23 sampling to confirm the SSTR expressing meningioma to be the FGF-23 secreting culprit lesion as many meningiomas are avid on SSTR-based imaging but may not be the source of FGF-23 (73). In summary, in the current era of SSTR-based imaging, the role of this modality seems to be limited to cases with multiple suspicious uptake sites, intracranial lesions consistent with meningioma, and lastly in imaging negative cases to identify a target for focused follow-up imaging.

Treatment

Primary modality

Complete surgical resection with adequate wide margin remains the treatment of choice in these tumors (3). This is supported in head and neck TIO cases where anatomical

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

sites less amenable for this approach have higher persistence or recurrence rate for example intracranial tumors. Hana *et al.* also reiterated this principle in their report on recurrent anterior skull base tumor with enbloc tumor removal followed by filling of the large skull base defect with pedicle subgaleal flap resulting in absence of recurrence over 25-month follow-up (93).

Stereotactic radiotherapy has been described in two cases as primary modality. Both patients had frontal lobe tumors and both refused surgery. One patient had lower plasma FGF-23 and oral phosphorous requirement at 6-month follow-up. The details of RT are not described in this case report (60). The second patient received 60 Gy of fractionated stereotactic radiotherapy over 5 weeks (73). On follow-up, patient was off phosphorus supplement and had normal FGF-23 concentration after 4 years. The tumor was stable with areas of multiple small hemorrhages. BMD improved by approximately 50% with no evident new fracture. As the tumors are slow growing, radiotherapy is deemed to be less effective (3).

Surgery combined with adjuvant post-op radiotherapy was used by John *et al.* in a case of invasive 'malignant schwannoma' (27). Over 2.5 years of follow-up, serum phosphorus normalized but 1,25(OH) vitamin D3 was persistently low. MRI showed no evidence of residual/recurrent tumor. Similarly, Lee *et al.* described a case where the patient received post-operative radiotherapy following incomplete removal of an ethmoid tumor, which resulted in normal serum phosphorus with no residual tumor on MRI after completion of RT (90).

In summary, although complete surgical excision remains the treatment modality of choice, in rare cases radiation therapy can be used with an expectant slow response.

Persistent/recurrent disease

Persistent/recurrent disease signifies failure of complete resection of the tumor after primary excision. This occurs more commonly in intracranial disease and oral cavity lesions where enbloc tumor removal is challenging and leads to higher surgical morbidity and complications. Serial biochemical follow-up is essential as true recurrences after complete biochemical resolution are known, but usually it is the recurrence of symptoms which brings the disease to surface.

After anatomic imaging to confirm the site of tumor recurrence, re-exploration of the surgical site along with attempted enbloc removal remains the preferred approach. Out of eleven patients with persistent/recurrent disease who have ANED on follow-up, eight have been treated with re-surgery alone.

In persistent cases multiple re-surgeries, radiotherapy, cinacalcet and octeotride have been used with limited success. Seufert *et al.* reported a patient with left thigh TIO localized on octreotide scinitigraphy having complete resolution of phosphaturia and normalization of serum phosphorus with 50–100 µg of octreotide thrice a day in preoperative setting (125). However, this initial success has not been replicated in subsequent studies (34, 126). Extrapolating from patients with hypoparathyroidism with elevated FGF-23 and serum phosphorus levels, Gellers *et al.* advocated for the use of cinacalcet in the treatment of TIO (127). But development of hypercalciuria and hypocalcemia limits the use of cinacalcet in this cohort. Disease stability with dasatinib has been reported (55). As these tumors also express SSTR, PRRT remains a potentially useful option in tumors showing Krenning III/IV uptake on ^{68}Ga-DOTATATE PET/CT (113). It has been more than a decade of successful utilization of two radiopeptides ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE for treatment of advanced neuroendocrine tumors (NETs) (128). After binding to SSTR these peptides are internalized in tumor cells and the released breakdown products in lysosomes mediate radioactivity-induced local damage (128). Apart from our case, we could not find any other experience with PRRT in TIO literature. In patients with persistent disease, treatment with oral phosphate supplements and calcitriol is continued for symptomatic improvement.

Metastases

Four cases of malignant TIO in head and neck region are reported so far. Three of them originated from oral cavity and one from mandible. Uramoto *et al.* described a case of malignant PMTMCT involving tongue with lymph node metastases treated with two surgeries followed by radiation therapy with persistent disease on last follow-up (39). Bergwitz *et al.* reported a patient with ameloblastic fibrosarcoma of mandible with pulmonary and lymph node metastases (61). Patient had multiple recurrences and was managed with repeated surgeries, and lastly cinacalcet with persistent hypophosphatemia. Fatani *et al.* reported an interesting case of malignant PMTMCT arising from oral cavity who after 17 years of follow-up developed lung metastases which were resected in addition to multiple surgeries for primary disease (71). Patient was normophosphatemic on follow-up. The fourth case of malignant PMTMCT was reported by Wasserman *et al.* (84).

https://ec.bioscientifica.com
https://doi.org/10.1530/EC-19-0341

The tumor involved nose, lip and mouth. No further follow-up/management details have been reported.

Histopathology

Weidner *et al.* initially proposed the term phosphaturic mesenchymal tumors (PMT) and their classification into four distinct subtypes: (I) mixed connective tissue variant (MCT), (II) osteoblastoma like, (III) Non-ossifying fibroma type, (IV) ossifying fibroma like (129). In 2004, Folpe *et al.* reviewed all previously published cases and found that they all belong to PMTMCT category (10). In this review we have reported the revised diagnosis as mentioned by Folpe *et al.* In 2018, Wu *et al.* described a new entity called "PMT mixed epithelial and connective tissue type" which is found exclusively in alveolar bone of maxilla and mandible (102). They found this tumor to be common in males and in patients <40 years of age. They have proposed a revised diagnosis of previously published six cases to this new entity, but we have reported them according to the original report. Apart from PMTs, other reported tumors in head and neck region causing TIO include meningioma, salivary basal cell adenoma, malignant schwannoma, ameloblastic fibrosarcoma, and spindle cell tumor with PMT features.

Study limitations

To our knowledge this is the largest review of TIO due to tumors located in head and neck region till date. The per-patient analysis method used in this study with minute detailing of all clinically relevant published aspects is the major strength of this study. There are several limitations in this study. As the review is a retrospective analysis of published case reports, all the limitations pertaining to retrospective studies apply to it. Additionally, many case reports lacked important clinical details as majority of them focused on pathology or imaging. A meticulous attempt was made to include all published literature regarding the subject but a few studies may not have been included.

Summary

TIO in the head and neck region is a rare disorder that warrants management by a multidisciplinary team including an endocrinologist, head and neck surgeon, radiologist, nuclear physicist and pathologist. Low phosphorus with elevated FGF-23 levels in a patient with clinical features of osteomalacia and/or mass in the head and neck region should be evaluated with Ga-DOTA-based PET/CT imaging. An alternative approach would be anatomical imaging followed by biopsy in a patient with local symptoms and clinically apparent swelling. Complete surgical excision with wide margin is of utmost importance in these cases resulting in dramatic clinical and biochemical normalcy. Clinical and biochemical follow-up is necessary even after documented cure as true recurrences have been reported. Whenever complete excision is not achieved, repeat surgical excision is recommended for accessible disease burden. In inoperable cases, radiotherapy, PRRT and medical management are suitable alternatives which should be decided by a multidisciplinary team on an individual basis. Although the tumor remains benign in most cases, one must remain vigilant in case of long-standing disease due to the reported risk of metastasis. Histopathological examination in most cases reveals PMTMCT, but other types are also seen.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research has been supported by Department of Endocrinology, Seth GS Medical College & KEM Hospital, Mumbai, India and Diamond Jubilee Society Trust (DJST), KEM Hospital, Mumbai, India.

References

1 Drezner MK. Tumor-induced osteomalacia. In *Primer on Metabolic Bone Diseases and Disorders of Mineral Metabolism*, 4th ed., ch 74, pp 331–337. Ed. MJ Favus. Philadelphia, PA, USA: Lippincott-Raven, 1999.

2 McCance R. Osteomalacia with Loosers nodes (Milkman's syndrome) due a raised resistance to vitamin D acquired about the age of 15 years. *Quarterly Journal of Medicine* 1947 **16** 33–46.

3 Chong WH, Molinolo AA, Chen CC & Collins MT. Tumor-induced osteomalacia. *Endocrine-Related Cancer* 2011 **18** R53–R77. (https://doi.org/10.1530/ERC-11-0006)

4 Jiang Y, Xia WB, Xing XP, Silva BC, Li M, Wang O, Zhang HB, Li F, Jing HL, Zhong DR, *et al*. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. *Journal of Bone and Mineral Research* 2012 **27** 1967–1975. (https://doi.org/10.1002/jbmr.1642)

5 Renton P & Shaw DG. Hypophosphatemic osteomalacia secondary to vascular tumous of bone and soft tissue. *Skeletal Radiology* 1976 **1** 21–24. (https://doi.org/10.1007/BF00347723)

6 Sweet RA, Males JL, Hamstra AJ & DeLuca HF. Vitamin D metabolite levels in oncogenic osteomalacia. *Annals of Internal Medicine* 1980 **93** 279–280. (https://doi.org/10.7326/0003-4819-93-2-279)

7 Nitzan DW, Marmary Y & Azaz B. Mandibular tumor-induced muscular weakness and osteomalacia. *Oral Surgery, Oral Medicine, and Oral Pathology* 1981 **52** 253–256. (https://doi.org/10.1016/0030-4220(81)90257-7)

8 Nomura G, Koshino Y, Morimoto H, Kida H, Nomura S & Tamai K. Vitamin D resistant hypophosphatemic osteomalacia associated with osteosarcoma of the mandible: report of a case. *Japanese Journal of Medicine* 1982 **21** 35–39. (https://doi.org/10.2169/internalmedicine1962.21.35)

9 Linsey M, Smith W, Yamauchi H & Bernstein L. Nasopharyngeal angiofibroma presenting as adult osteomalacia: case report and review of the literature. *Laryngoscope* 1983 **93** 1328–1331. (https://doi.org/10.1002/lary.1983.93.10.1328)

10 Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, Econs MJ, Inwards CY, Jan de Beur SM, Mentzel T, *et al.* Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *American Journal of Surgical Pathology* 2004 **28** 1–30. (https://doi.org/10.1097/00000478-200401000-00001)

11 Seshadri MS, Cornish CJ, Mason RS & Posen S. Parathyroid hormone like bioactivity in tumours from patients with oncogenic osteomalacia. *Clinical Endocrinology* 1985 **23** 689–697. (https://doi.org/10.1111/j.1365-2265.1985.tb01130.x)

12 Jefferis AF, Taylor PCA & Walsh-Waring GP. Tumour associated hypophosphatemic osteomalacia occurring in a patient with an odontogenic tumour of the maxilla. *Journal of Laryngology and Otology* 1985 **99** 1011–1017. (https://doi.org/10.1017/s0022215100098091)

13 Weidner N, bar RS, Weiss D & Strottmann MP. Neoplastic pathology of oncogenic osteomalacia/rickets. *Cancer* 1985 **55** 1691–1705. (https://doi.org/10.1002/1097-0142(19850415)55:8<1691::aid-cncr2820550814>3.0.co;2-s)

14 Lee HK, Sung WW, Solodnik P & Shimshi M. Bone scan in tumour-induced osteomalacia. *Journal of Nuclear Medicine* 1995 **36** 247–249.

15 Catalano PJ, Brandwein M, Shah DK, Urken ML, Lawson W & Biller HF. Sinonasal hemangiopericytomas: a clinicopathologic and immunohistochemical study of seven cases. *Head and Neck* 1996 **18** 42–53. (https://doi.org/10.1002/(SICI)1097-0347(199601/02)18:1<42::AID-HED6>3.0.CO;2-Z)

16 Wilkins GE, Granleese S, Hegele RG, Holden J, Anderson DW & Bondy GP. Oncogenic osteomalacia: evidence for a humoral phosphaturic factor. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 1628–1634. (https://doi.org/10.1210/jcem.80.5.7745010)

17 David K, Revesz T, Kratimenos G, Krausz T & Crockard HA. Oncogenic osteomalacia associated with a meningeal phosphaturic mesenchymal tumour. *Journal of Neurologicalsurgery* 1996 **84** 288–292.

18 Kim YG, Choi YS, Lee SC & Ryu DM. Tumour-induced osteomalacia associated with lesions in the oral and maxillofacial region: report of two cases. *Journal of Oral and Maxillofacial Surgery* 1996 **54** 1352–1357. (https://doi.org/10.1016/s0278-2391(96)90497-8)

19 Avila NA, Skarulis M, Rubino DM & Doppman JL. Oncogenic osteomalacia: lesion detection by MR skeletal survey. *American Journal of Roentgenology* 1996 **167** 343–345. (https://doi.org/10.2214/ajr.167.2.8686600)

20 Yang IM, Park YK, Hyun YJ, Kim DY, Woo JT, Kim SW, Kim JW, Kim YS & Choi YK. Oncogenic osteomalacia caused by a phosphaturic mesenchymal tumour of the oral cavity: a case report. *Korean Journal of Internal Medicine* 1997 **12** 89–95. (https://doi.org/10.3904/kjim.1997.12.1.89)

21 Gonzalez-Compta X, Manos-Pujol M, Foglia-Fernandez M, Peral E, Condom E, Claveguera T & Dicenta-Sousa M. Oncogenic osteomalacia: case report and review of head and neck associated tumours. *Journal of Laryngology and Otology* 1998 **112** 389–392. (https://doi.org/10.1017/s0022215100140551)

22 Ohashi K, Ohnishi T, Ishikawa T, Tani H, Uesugi K & Takagi M. Oncogenic osteomalacia presenting as bilateral stress fractures of the tibia. *Skeletal Radiology* 1999 **28** 46–48. (https://doi.org/10.1007/s002560050471)

23 Clunie GPR, Fox PE & Stamp TCB. Four cases of acquired hypophosphatemic (oncogenic) osteomalacia. Problems of diagnosis, treatment and long-term management. *Rheumatology* 2000 **39** 1415–1421. (https://doi.org/10.1093/rheumatology/39.12.1415)

24 Sandhu FA & Martuza RL. Craniofacial hemangiopericytoma associated with oncogenic osteomalacia: case report. *Journal of Neuro-Oncology* 2000 **46** 241–247. (https://doi.org/10.1023/a:1006352106762)

25 Reyes-Mugica M, Arnsmeier SL, Backeljauw PF, Persing J, Ellis B & Carpenter TO. Phosphaturic mesenchymal tumour-induced rickets. *Pediatric and Developmental Pathology* 2000 **3** 61–69. (https://doi.org/10.1007/s100240050008)

26 Kawai Y, Morimoto S, Sakaguchi K, Yoshino H, Yotsui T, Hirota S, Inohara H, Nakagawa T, Hattori K, Kubo T, *et al.* Oncogenic osteomalacia secondary to nasal tumour with decreased urinary excretion of cAMP. *Journal of Bone and Mineral Metabolism* 2001 **19** 61–64. (https://doi.org/10.1007/s007740170062)

27 John MR, Wickert H, Zaar K, Jonsson KB, Grauer A, Ruppersberger P, Schmidt-Gayk H, Murer H, Ziegler R & Blind E. A case of neuroendocrine oncogenic osteomalacia associated with a PHEX and fibroblast growth factor-23 expressing sinusoidal malignant schwannoma. *Bone* 2001 **29** 393–402. (https://doi.org/10.1016/s8756-3282(01)00586-5)

28 Reis-Filho JS, Paiva ME & Lopes JM. August 2003: 47-year-old female with a 7-year history of osteomalacia and hypophosphatemia. *Brain Pathology* 2004 **14** 111–112, 115. (https://doi.org/10.1111/j.1750-3639.2004.tb00505.x)

29 Fuentealba C, Pinto D, Ballesteros F, Pacheco D, Boettiger O, Soto N, Fernandez W, Gabler F, Gonzales G & Reginato AJ. Oncogenic hypophosphatemic osteomalacia associated with a nasal hemangiopericytoma. *Journal of Clinical Rheumatology* 2003 **9** 373–379. (https://doi.org/10.1097/01.rhu.0000101906.15276.ed)

30 Ungari C, Rocchi G, Rinna C, Agrillo A, Lattanzi A & Pagnoni M. Hypophosphaturic mesenchymal tumour of the ethmoid associated with oncogenic osteomalacia. *Journal of Craniofacial Surgery* 2004 **15** 523–527.

31 Dupond JL, Mahammedi H, Magy N, Blagosklonov O, Meaux-Ruault N & Kantelip B. Detection of a mesenchymal tumor responsible for hypophosphatemic osteomalacia using FDG-PET. *European Journal of Internal Medicine* 2005 **16** 445–446. (https://doi.org/10.1016/j.ejim.2005.07.003)

32 Kaylie DM, Jackson CG & Gardner EK. Oncogenic osteomalacia caused by phosphaturic mesenchymal tumor of the temporal bone. *Otolaryngology–Head and Neck Surgery* 2006 **135** 653–654. (https://doi.org/10.1016/j.otohns.2005.03.086)

33 Inokuchi G, Tanimoto H, Ishida H, Sugimoto T, Yamauchi M, Miyauchi A & Nibu K. A paranasal tumor associated with tumor-induced osteomalacia. *Laryngoscope* 2006 **116** 1930–1933. (https://doi.org/10.1097/01.mlg.0000231295.67060.89)

34 Yoshioka K, Nagata R, Ueda M, Yamaguchi T, Konishi Y, Hosoi M, Inoue T, Yamanaka K, Iwai Y & Sato T. Phosphaturic mesenchymal tumor with symptoms related to osteomalacia that appeared one year after tumorectomy. *Internal Medicine* 2006 **45** 1157–1160. (https://doi.org/10.2169/internalmedicine.45.1797)

35 Koriyama N, Nishimoto K, Kodama T, Nakazaki M, Kurono Y, Yoshida H & Tei C. Oncogenic osteomalacia in a case with a maxillary sinus mesenchymal tumor. *American Journal of the Medical Sciences* 2006 **332** 142–147. (https://doi.org/10.1097/00000441-200609000-00010)

36 Elston MS, Stewart IJ, Clifton-Bligh R & Conaglen JV. A case of oncogenic osteomalacia with preoperative secondary hyperparathyroidism: description of the biochemical response of FGF23 to octreotide therapy and surgery. *Bone* 2007 **40** 236–241. (https://doi.org/10.1016/j.bone.2006.07.027)

37 Beech TJ, Rokade A, Gittoes N & Johnson AP. A hemangiopericytoma of the ethmoid sinus causing oncogenic osteomalacia: a case report and review of the literature. *International Journal of Oral and*

Maxillofacial Surgery 2007 **36** 956–958. (https://doi.org/10.1016/j.ijom.2007.03.005)
38 Ahn JM, Kim HJ, Cha CM, Kim J, Yim SG & Kim HJ. Oncogenic osteomalacia: induced by tumour, cured by surgery. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2007 **103** 636–641. (https://doi.org/10.1016/j.tripleo.2005.12.027)
39 Uramoto N, Furukawa M & Yoshizaki T. Malignant phosphaturic mesenchymal tumor, mixed connective tissue variant of the tongue. *Auris, Nasus, Larynx* 2009 **36** 104–105. (https://doi.org/10.1016/j.anl.2008.01.003)
40 Lewiecki EM, Urig EJ & Williams RC. Tumor-induced osteomalacia: lessons learned. *Arthritis and Rheumatism* 2008 **58** 773–777. (https://doi.org/10.1002/art.23278)
41 Kenealy H, Holdaway I & Grey A. Occult nasal sinus tumours causing oncogenic osteomalacia. *European Journal of Internal Medicine* 2008 **19** 516–519. (https://doi.org/10.1016/j.ejim.2008.01.011)
42 Yun KI, Kim DH & Pyo SW. A phosphaturic mesenchymal tumor of the floor of the mouth with oncogenic osteomalacia: report of a case. *Journal of Oral and Maxillofacial Surgery* 2009 **67** 402–405. (https://doi.org/10.1016/j.joms.2008.01.007)
43 Woo VL, Landesberg R, Imel EA, Singer SR, Folpe AL, Econs MJ, Kim T, Harik LR & Jacobs TP. Phosphaturic mesenchymal tumor, mixed connective tissue variant, of the mandible: report of a case and review of the literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2009 **108** 925–932. (https://doi.org/10.1016/j.tripleo.2009.07.005)
44 Savage CR & Zimmer LA. Oncogenic osteomalacia from pterygopalatine fossa mass. *Journal of Laryngology and Otology* 2009 **123** 1052–1054. (https://doi.org/10.1017/S0022215109004927)
45 Kurien R, Manipadam MT & Rupa V. Oncogenic osteomalacia in a patient with an ethmoid sinus tumour. *Journal of Laryngology and Otology* 2010 **124** 799–803. (https://doi.org/10.1017/S0022215109992313)
46 Gupta R, Sharma A, Ksh A, Khadgawat R & Dinda AK. Phosphaturic mesenchymal tumour of the sinonasal tract. *Acta Endocrinologica (Bucharest)* 2009 5 537–541. (https://doi.org/10.4183/aeb.2009.537)
47 Gore MO, Welch BJ, Geng W, Kabbani W, Maalouf NM, Zerwekn JE, Moe OW & Sakhaee K. Renal phosphate wasting due to tumor-induced osteomalacia: a frequently delayed diagnosis. *Kidney International* 2009 **76** 342–347. (https://doi.org/10.1038/ki.2008.355)
48 Kobayashi K, Nakao K, Kawai K, Ito K, Hukumoto S, Asakage T, Oota S & Motoi R. Tumor-induced osteomalacia originating from the temporal bone: a case report. *Head and Neck* 2011 **33** 1072–1075. (https://doi.org/10.1002/hed.21355)
49 Shelekhova KV, Kazakov DV & Michal M. Sinonasal phosphaturic mesenchymal tumor (mixed connective tissue variant): report of 2 cases. *American Journal of Surgical Pathology* 2010 **34** 596–597. (https://doi.org/10.1097/PAS.0b013e3181d594fa)
50 Pedrazzoli M, Colletti G, Ferrari M, Rossetti G, Moneghini L & Autelitano L. Mesenchymal phosphaturic neoplasm in the maxillary sinus: a case report. *International Journal of Oral and Maxillofacial Surgery* 2010 **39** 1027–1032. (https://doi.org/10.1016/j.ijom.2010.04.039)
51 Mori Y, Ogasawara T, Motoi T, Shimizu Y, Chikazu D, Tamura K, Fukumoto S & Takato T. Tumor-induced osteomalacia associated with a maxillofacial tumor producing fibroblast growth factor 23: report of a case and review of the literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics* 2010 **109** e57–e63. (https://doi.org/10.1016/j.tripleo.2009.10.052)
52 Parshwanath HA, Kulkarni PR, Rao R, Joshi SK & Patil P. Phosphaturic mesenchymal tumor of ethmoid sinus. *Indian Journal of Pathology and Microbiology* 2010 **53** 384–385. (https://doi.org/10.4103/0377-4929.64317)
53 Battoo AJ, Salih S, Unnikrish AG, Jojo A, Bahadur S, Iyer S & Kuriakose MA. Oncogenic osteomalacia from nasal cavity giant cell tumor. *Head and Neck* 2012 **34** 454–457. (https://doi.org/10.1002/hed.21562)
54 Arnaoutakis D & Naseri I. Sinonasal phosphaturic mesenchymal tumor: a rare and misinterpreted entity. *Journal of Neurological Surgery Reports* 2015 **76** e233–e238. (https://doi.org/10.1055/s-0035-1562852)
55 Peters KB, McLendon R, Morse MA & Vredenburgh JJ. Treatment of recurrent intracranial hemangiopericytoma with SRC-related tyrosine kinase targeted therapy: a case report. *Case Reports in Oncology* 2010 **3** 93–97. (https://doi.org/10.1159/000307468)
56 Akhter M, Sugrue PA, Bains R & Khavkin YA. Oncogenic osteomalacia of the cervical spine: a rare case of curative resection and reconstruction. *Journal of Neurosurgery. Spine* 2011 **14** 453–456. (https://doi.org/10.3171/2010.11.SPINE09750)
57 Xian-Ling W, Jian-Ming B, Wen-wen Z, Zhao-Hui L, Jing-Tao D, Ju-Ming L & Yi-Ming M. Osteomalacia caused by tumors in facies cranii mimicking rheumatoid arthritis. *Rheumatology International* 2012 **32** 2573–2576. (https://doi.org/10.1007/s00296-011-2018-4)
58 Guglielmi G, Bisceglia M, Scillitani A & Folpe AL. Oncogenic osteomalacia due to phosphaturic mesenchymal tumor of the craniofacial sinuses. *Clinical Cases in Mineral and Bone Metabolism* 2011 **8** 45–49.
59 Uno T, Kawai K, Kunii N, Fukumoto S, Shibahara J, Motoi T & Saito N. Osteomalacia caused by skull base tumors: report of 2 cases. *Neurosurgery* 2011 **69** E239–E244; discussion E244. (https://doi.org/10.1227/NEU.0b013e31821867f7)
60 Andreupoulou P, Dumitrescu CE, Kelly MH, Brillante BA, Peck CMC, Wodajo FM, Chang R & Collins MT. Selective venous catheterization for the localization of phosphaturic mesenchymal tumors. *Journal of Bone and Mineral Research* 2011 **6** 1295–1302.
61 Bergwitz C, Collins MT, Kamath RS & Rosenberg AE. Case 33–2011: a 56-year-old man with hypophosphatemia. *New England Journal of Medicine* 2011 **365** 1625–1635. (https://doi.org/10.1056/NEJMcpc1104567)
62 Monappa V, Naik AM, Mathew M, Rao L, Rao SK, Ramachandra L & Padmapriya J. Phosphaturic mesenchymal tumour of the mandible – the useful criteria for a diagnosis on fine needle aspiration cytology. *Cytopathology* 2014 **25** 54–56. (https://doi.org/10.1111/cyt.12030)
63 Chokyu I, Ishibashi K, Goto T & Ohata K. Oncogenic osteomalacia associated with mesenchymal tumor in the middle cranial fossa: a case report. *Journal of Medical Case Reports* 2012 **6** 181. (https://doi.org/10.1186/1752-1947-6-181)
64 Chiam P, Tan HC, Bee YM & Chandran M. Oncogenic osteomalacia – hypophosphatemic spectrum from benignancy to malignancy. *Bone* 2013 **53** 182–187. (https://doi.org/10.1016/j.bone.2012.11.040)
65 Cho S, Do NY, Yu SW & Choi JY. Nasal hemangiopericytoma causing oncogenic osteomalacia. *Clinical and Experimental Otolaryngology* 2012 **3** 173–176.
66 Burnand H, Samuels A, Hagan I, Sawant N & Mutimer J. Bilateral subtrochanteric fractures in tumor-induced osteomalacia caused by a nasal hemangiopericytoma. *Hip International* 2012 **22** 227–229. (https://doi.org/10.5301/HIP.2012.9235)
67 Brandwein-Gensler M & Siegal GP. Striking pathology gold: a singular experience with daily reverberations: sinonasal hemangiopericytoma (glomangiopericytoma) and oncogenic osteomalacia. *Head and Neck Pathology* 2012 **6** 64–74. (https://doi.org/10.1007/s12105-012-0337-8)
68 Munoz J, Ortega RM, Celzo F & Donthireddy V. Tumour-induced osteomalacia. *BMJ Case Reports* 2012 **2012** bcr0320125975. (https://doi.org/10.1136/bcr.03.2012.5975)
69 Chang CV, Conde SJ, Luvizotto RAM, Nunes VS, Bonates MC, Felicio AC, Lindsey SC, Moraes FH, Tagliarini JV, Mazeto GMFS, *et al.* Oncogenic osteomalacia: loss of hypophosphatemia might be the key to avoid misdiagnosis. *Arquivos Brasileiros de Endocrinologia e Metabologia* 2012 **56** 570–573. (https://doi.org/10.1590/S0004-27302012000800018)

70 Jiang Y, Xia WB, Xing XP, Silva BC, Li M, Wang O, Zhang HB, Li F, Jing HL, Zhong DR, *et al*. Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature. *Journal of Bone and Mineral Research* 2012 **27** 1967–1975. (https://doi.org/10.1002/jbmr.1642)

71 Fatani HA, Sunbuli M, Lai SY & Bell D. Phosphaturic mesenchymal tumor: a report of 6 patients treated at a single institution and comparison with reported series. *Annals of Diagnostic Pathology* 2013 **17** 319–321. (https://doi.org/10.1016/j.anndiagpath.2012.06.005)

72 Mathis DA, Stehel EJ, Beshay JE, Mickey BE, Folpe AL & Raisanen J. Intracranial phosphaturic mesenchymal tumors: report of 2 cases. *Journal of Neurosurgery* 2013 **118** 903–907. (https://doi.org/10.3171/2012.12.JNS12598)

73 Tarasova VD, Trepp-Carrasco AG, Thompson R, Recker RR, Chong WH, Collins MT & Armas LA. Successful treatment of tumor-induced osteomalacia due to an intracranial tumor by fractionated stereotactic radiotherapy. *Journal of Clinical Endocrinology and Metabolism* 2013 **98** 4267–4272. (https://doi.org/10.1210/jc.2013-2528)

74 Papierska L, Ćwikła JB, Misiorowski W, Rabijewski M, Sikora K & Wanyura H. Unusual case of phosphaturic mesenchymal tumor. *Polskie Archiwum Medycyny Wewnetrznej* 2013 **123** 255–256. (https://doi.org/10.20452/pamw.1738)

75 Lee GG, Dhong HJ, Park YS & Ko YH. Sinonasal glomangiopericytoma causing oncogenic osteomalacia. *Clinical and Experimental Otorhinolaryngology* 2014 **7** 145–148. (https://doi.org/10.3342/ceo.2014.7.2.145)

76 Allevi F, Rabbiosi D, Mandala M & Colletti G. Mesenchymal phosphaturic tumour: early detection of recurrence. *BMJ Case Reports* 2014 **2014** bcr2013202827. (https://doi.org/10.1136/bcr-2013-202827)

77 Annamalai AK, Sampathkumar K, Kane S, Shetty NS, Kulkarni S, Rangarajan V, Purandare N, Pai PS, Mahuvakar AD, Shanthi R, *et al*. Needles in the haystack – synchronous multifocal tumor-induced osteomalacia. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 390–393. (https://doi.org/10.1210/jc.2015-3854)

78 Okamiya T, Takahashi K, Kamada H, Hirato J, Motoi T, Fukumoto S & Chikamatsu K. Oncogenic osteomalacia caused by an occult paranasal sinus tumor. *Auris, Nasus, Larynx* 2015 **42** 167–169. (https://doi.org/10.1016/j.anl.2014.10.001)

79 Mok Y, Lee JC, Lum JHY & Petersson F. From epistaxis to bone pain – report of two cases illustrating the clinicopathological spectrum of phosphaturic mesenchymal tumor with fibroblast growth factor receptor 1 immunohistochemical and cytogenetic analyses. *Histopathology* 2016 **68** 925–930. (https://doi.org/10.1111/his.12872)

80 Fernandez-Cooke E, Cruz-Rojo J, Gallego C, Romance AI, Mosqueda-Pena R, Almaden Y & del Pozo JS. Tumor-induced rickets in a child with a central giant cell granuloma: a case report. *Pediatrics* 2015 **135** e1518–e1523. (https://doi.org/10.1542/peds.2014-2218)

81 Fathalla H, Cusimano M, Di leva A, Karamchandani J, Fung R & Kovacs K. Osteomalacia-inducing tumors of the brain: a case report, review and a hypothesis. *World Neurosurgery* 2015 **84** 189.e1–189.e5. (https://doi.org/10.1016/j.wneu.2015.02.030)

82 Ray S, Chakraborty PP, Biswas K, Ghosh S, Mukhopadhyay S & Chowdhury S. A case of oncogenic osteomalacia due to occult nasal sinus tumor. *Clinical Cases in Mineral and Bone Metabolism* 2015 **12** 65–68. (https://doi.org/10.11138/ccmbm/2015.12.1.065)

83 Qari H, Hamao-Sakamoto A, Fuselier C, Cheng YSL, Kessler H & Wright J. Phosphaturic mesenchymal tumor: 2 new oral cases and review of 53 cases in the head and neck. *Head and Neck Pathology* 2016 **10** 192–200. (https://doi.org/10.1007/s12105-015-0668-3)

84 Wasserman JK, Purgina B, Lai CK, Gravel D, Mahaffey A, Bell D & Chiosea SI. Phosphaturic mesenchymal tumor involving the head and neck: a report of five cases with FGFR1 fluorescence in situ hybridization analysis. *Head and Neck Pathology* 2016 **10** 279–285. (https://doi.org/10.1007/s12105-015-0678-1)

85 Mani MK & Panigrahi MK. Unusual calvarial tumour-oncogenic osteomalacia. *British Journal of Neurosurgery* 2017 **31** 495–496. (https://doi.org/10.3109/02688697.2016.1161165)

86 Yu WJ, He JW, Fu WZ, Wang C & Zhang ZL. Reports of 17 Chinese patients with tumor-induced osteomalacia. *Journal of Bone and Mineral Metabolism* 2017 **35** 298–307. (https://doi.org/10.1007/s00774-016-0756-9)

87 Takashi Y, Kinoshita Y, Ito N, Taguchi M, Takahashi M, Egami N, Tajima S, Nangaku M & Fukumoto S. Tumor-induced osteomalacia caused by a parotid tumor. *Internal Medicine* 2017 **56** 535–539. (https://doi.org/10.2169/internalmedicine.56.7565)

88 Gresham MS, Shen S, Zhang YJ & Gallagher K. Anterior skull base glomangioma-induced osteomalacia. *Journal of Neurological Surgery Reports* 2017 **78** e9–e11. (https://doi.org/10.1055/s-0036-1597599)

89 Agaimy A, Michal M, Chiosea S, Petersson F, Hadravsky L, Kristiansen G, Horch RE, Schmolders J, Hartmann A, Haller F, *et al*. Phosphaturic mesenchymal tumors: clinicopathologic, immunohistochemical and molecular analysis of 22 cases expanding their morphologic and immunophenotypic spectrum. *American Journal of Surgical Pathology* 2017 **41** 1371–1380. (https://doi.org/10.1097/PAS.0000000000000890)

90 Lee JY, Park HS, Han S, Lim JK, Hong N, Park SI & Rhee Y. Localization of oncogenic osteomalacia by systemic venous sampling of fibroblast growth factor 23. *Yonsei Medical Journal* 2017 **58** 981–987. (https://doi.org/10.3349/ymj.2017.58.5.981)

91 Schober HC, Kneitz C, Fieber F, Hesse K & Schroeder H. Selective blood sampling for FGF-23 in tumor-induced osteomalacia. *Endocrinology, Diabetes and Metabolism Case Reports* 2017 **2017** 1. (https://doi.org/10.1530/EDM-17-0006)

92 Zuo QY, Wang H, Li W, Niu XH, Huang YH, Chen J, You YH, Liu BY, Cui AM & Deng W. Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients. *BMC Musculoskeletal Disorders* 2017 **18** 403. (https://doi.org/10.1186/s12891-017-1756-1)

93 Hana T, Tanaka S, Nakatomi H, Shojima M, Fukumoto S, Ikemura M & Saito N. Definitive surgical treatment of osteomalacia induced by skull base tumor and determination of the half-life of serum fibroblast growth factor 23. *Endocrine Journal* 2017 **64** 1033–1039. (https://doi.org/10.1507/endocrj.EJ17-0177)

94 Chanukya GV, Mengade M, Goud J, Rao IS & Jain A. Tumor-induced osteomalacia: a Sherlock Holmes approach to diagnosis and management. *Annals of Maxillofacial Surgery* 2017 **7** 143–147. (https://doi.org/10.4103/ams.ams_123_16)

95 Gonzalez G, Baudrand R, Sepulveda MF, Vucetich N, Guarda FJ, Villanueva P, Contreras O, Villa A, Salech F, Toro L, *et al*. Tumor-induced osteomalacia: experience from a South American academic centre. *Osteoporosis International* 2017 **28** 2187–2193. (https://doi.org/10.1007/s00198-017-4007-2)

96 Singh D, Chopra A, Ravina M, Kongara S, Bhatia E, Kumar N, Gupta S, Yadav S, Dabadghao P, Yadav R, *et al*. Oncogenic osteomalacia: role of Ga-68 DOTANOC PET/CT scan in identifying the culprit lesion and its management. *British Journal of Radiology* 2017 **90** 20160811. (https://doi.org/10.1259/bjr.20160811)

97 Pelletier K, Troyanov S, Guite JF, Sainte-Marie LG, Roberge D & Lessard M. Localization of ectopic fibroblast growth factor 23 production in tumor-induced osteomalacia using selective venous samplings. *Clinical Nephrology* 2017 **87** 107–110. (https://doi.org/10.5414/CN108981)

98 Mumford E, Marks J, Wagner T, Gallimore A, Gane S & Walsh SB. Oncogenic osteomalacia: diagnosis, localisation, and cure. *Lancet Oncology* 2018 **19** e365. (https://doi.org/10.1016/S1470-2045(18)30276-6)

99 Villepelet A, Casiraghi O, Temam S & Moya-Plana A. Ethmoid tumor and oncogenic osteomalacia: case report and review of the literature. *European Annals of Otorhinolaryngology, Head and Neck Diseases* 2018 **135** 365–369. (https://doi.org/10.1016/j.anorl.2018.07.001)

100 Pelo S, Gasparini G, Garagiola U, D'Amato G, Saponaro G, Doneddu P, Todaro M & Moro A. Phosphaturic mesenchymal tumor, an unusual localization in head and neck. *Journal of Surgical Case Reports* 2018 **2018** rjy091. (https://doi.org/10.1093/jscr/rjy091)

101 He Q, Xu Z, Zhang B, Hu W & Zhang X. Tumor-induced osteomalacia caused by a parotid basal cell adenoma detected by 68Ga-DOTANOC PET/CT. *Clinical Nuclear Medicine* 2018 **43** e198–e199. (https://doi.org/10.1097/RLU.0000000000002076)

102 Wu H, Bui MM, Zhou L, Li D, Zhang H & Zhong D. Phosphaturic mesenchymal tumor with an admixture of epithelial and mesenchymal elements in the jaws: clinicopathological and immunohistochemical analysis of 22 cases with literature review. *Modern Pathology* 2019 **32** 189–204. (https://doi.org/10.1038/s41379-018-0100-0)

103 Ding J, Hu G, Wang L, Li F & Huo L. Increased activity due to fractures does not significantly affect the accuracy of 68Ga-DOTATATE PET/CT in the detection of culprit tumor in the evaluation of tumor-induced osteomalacia. *Clinical Nuclear Medicine* 2018 **43** 880–886. (https://doi.org/10.1097/RLU.0000000000002290)

104 Mishra T, Desouza MA, Patel K & Mazumdar GA. Phosphaturic mesenchymal tumors involving skull bones: report of two rare cases. *Asian Journal of Neurosurgery* 2019 **14** 253–255. (https://doi.org/10.4103/ajns.AJNS_176_17)

105 Li J, Huang Y, Yang F, Zhang Q, Chen D & Wang Q. Sinonasal hemangiopericytoma caused hypophosphatemic osteomalacia: a case report. *Medicine* 2018 **97** e13849. (https://doi.org/10.1097/MD.0000000000013849)

106 Acharya RP, Won AM, Moon BS, Flint JH, Roubaud MS, Williams MD, Hessel AC, Murphy Jr WA, Chambers MS & Gagel RF. Tumor-induced hypophosphatemic osteomalacia caused by a mesenchymal tumor of the mandible managed by a segmental mandibulectomy and microvascular reconstruction with a free fibula flap. *Head and Neck* 2019 **41** E93–E98. (https://doi.org/10.1002/hed.25657)

107 Kurien R, Rupa V & Thomas M. Varied presentation of sinonasal phosphaturic mesenchymal tumour: report of a case series with follow-up. *European Archives of Oto-Rhino-Laryngology* 2019 **276** 1677–1684. (https://doi.org/10.1007/s00405-019-05341-8)

108 Paul J, Cherian KE, Kapoor N & Paul TV. Treating osteoporosis: a near miss in an unusual case of FGF-23 mediated bone loss. *BMJ Case Reports* 2019 **12** e228375. (https://doi.org/10.1136/bcr-2018-228375)

109 Pal R, Bhadada SK, Singhare A, Bhansali A, Kamalanathan S, Chadha M, Chauhan P, Sood A, Dhiman V, Sharma DC, *et al.* Tumor-induced osteomalacia: experience from three tertiary care centers in India. *Endocrine Connections* 2019 **8** 266–276. (https://doi.org/10.1530/EC-18-0552)

110 Jadhav S, Kasaliwal R, Lele V, Rangarajan V, Chandra P, Shah H, Malhotra G, Jagtap VS, Budyal S, Lila AR, *et al.* Functional imaging in primary tumour-induced osteomalacia: relative performance of FDG PET/CT vs somatostatin receptor-based functional scans: a series of nine patients. *Clinical Endocrinology* 2014 **81** 31–37. (https://doi.org/10.1111/cen.12426)

111 Agrawal K, Bhadada S, Mittal BR, Shukla J, Sood A, Bhattacharya A & Bhansali A. Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia. *Clinical Nuclear Medicine* 2015 **40** e6–e10. (https://doi.org/10.1097/RLU.0000000000000460)

112 El-Maouche D, Sadowski SM, Papadakis GZ, Guthrie L, Cottle-Delisle C, Merkel R, Millo C, Chen CC, Kebebew E & Collins MT. 68Ga-DOTATATE for tumor localization in tumor-induced osteomalacia. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 3575–3581. (https://doi.org/10.1210/jc.2016-2052)

113 Basu S & Fargose P. 177Lu-DOTATATE PRRT in recurrent skull-base phosphaturic mesenchymal tumor causing osteomalacia: a potential application of PRRT beyond neuroendocrine tumors. *Journal of Nuclear Medicine Technology* 2016 **44** 248–250. (https://doi.org/10.2967/jnmt.116.177873)

114 Kane SV, Kakkar A, Oza N, Sridhar E & Pai PS. Phosphaturic mesenchymal tumor of the nasal cavity and paranasal sinuses: a clinical curiosity presenting a diagnostic challenge. *Auris, Nasus, Larynx* 2018 **45** 377–383. (https://doi.org/10.1016/j.anl.2017.05.006)

115 Feng J, Jiang Y, Wang O, Li M, Xing X, Huo L, Li F, Yu W, Zhong DR, Jin J, *et al.* The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases. *Endocrine Journal* 2017 **64** 675–683. (https://doi.org/10.1507/endocrj.EJ16-0587)

116 Khosravi A, Cutler CM, Kelly MH, Chang R, Royal RE, Sherry RM, Wodajo FM, Fedarko NS & Collins MT. Determination of the elimination half-life of fibroblast growth factor-23. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 2374–2377. (https://doi.org/10.1210/jc.2006-2865)

117 Takeuchi Y, Suzuki H, Ogura S, Imai R, Yamazaki Y, Yamashita T, Miyamoto Y, Okazaki H, Nakamura K, Nakahara K, *et al.* Venous sampling for fibroblast growth factor-23 confirms preoperative diagnosis of tumor-induced osteomalacia. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3979–3982. (https://doi.org/10.1210/jc.2004-0406)

118 Minisola S, Peacock M, Fukumoto S, Cipriani C, Pepe J, Tella SH & Collins MT. Tumour-induced osteomalacia. *Nature Reviews Disease Primers* 2017 **3** 17044. (https://doi.org/10.1038/nrdp.2017.44)

119 Reubi JC, Waser B, Schaer JC & Laissue JA. Somatostatin receptor sst1–sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. *European Journal of Nuclear Medicine* 2001 **28** 836–846. (https://doi.org/10.1007/s002590100541)

120 de Beur SMJ, Streeten EA, Civelek AC, McCarthy EF, Uribe L, Marx SJ, Onobrakpeya O, Raisz LG, Watts NB, Sharon M, *et al.* Localisation of mesenchymal tumours by somatostatin receptor imaging. *Lancet* 2002 **359** 761–763. (https://doi.org/10.1016/S0140-6736(02)07846-7)

121 Kimizuka T, Ozaki Y & Sumi Y. Usefulness of 201 Tl and 99m Tc MIBI scintigraphy in a case of oncogenic osteomalacia. *Annals of Nuclear Medicine* 2004 **18** 63–67. (https://doi.org/10.1007/BF02985616)

122 Dupond JL, Mahammedi H, Prie D, Collin F, Gil H, Blagosklonov O, Ricbourg B, Meaux-Ruault N & Kantelip B. Oncogenic osteomalacia: diagnostic importance of fibroblast growth factor 23 and F-18 fluorodeoxyglucose PET/CT scan for the diagnosis and follow-up in one case. *Bone* 2005 **36** 375–378. (https://doi.org/10.1016/j.bone.2005.01.001)

123 Breer S, Brunkhorst T, Beil FT, Peldschus K, Heiland M, Klutmann S, Barvencik F, Zustin J, Gratz KF & Amling M. 68Ga DOTATATE PET/CT allows tumor localization in patients with tumor-induced osteomalacia but negative 111In-octreotide SPECT/CT. *Bone* 2014 **64** 222–227. (https://doi.org/10.1016/j.bone.2014.04.016)

124 Zhang J, Zhu Z, Zhong D, Dang Y, Xing H, Du Y, Jing H, Qiao Z, Xing X, Zhuang H, *et al.* 68Ga DOTATATE PET/CT is an accurate imaging modality in the detection of culprit tumors causing osteomalacia. *Clinical Nuclear Medicine* 2015 **40** 642–646. (https://doi.org/10.1097/RLU.0000000000000854)

125 Seufert J, Ebert K, Müller J, Eulert J, Hendrich C, Werner E, Schütze N, Schulz G, Kenn W, Richtmann H, *et al.* Octreotide therapy for tumor-induced osteomalacia. *New England Journal of Medicine* 2001 **345** 1883–1888. (https://doi.org/10.1056/NEJMoa010839)

126 Ovejero D, El-Maouche D, Brillante BA, Khosravi A, Gafni RI & Collins MT. Octreotide is ineffective in treating tumor-induced osteomalacia: results of a short-term therapy. *Journal of Bone and*

Mineral Research 2017 **32** 1667–1671. (https://doi.org/10.1002/jbmr.3162)

127 Geller JL, Khosravi A, Kelly MH, Riminucci M, Adams JS & Collins MT. Cinacalcet in the management of tumor-induced osteomalacia. *Journal of Bone and Mineral Research* 2007 **22** 931–937. (https://doi.org/10.1359/jbmr.070304)

128 Cives M & Strosberg J. Radionuclide therapy for neuroendocrine tumors. *Current Oncology Reports* 2017 **19** 9. (https://doi.org/10.1007/s11912-017-0567-8)

129 Weidner N. Review and update: oncogenic osteomalacia-rickets. *Ultrastructural Pathology* 1991 **15** 317–333. (https://doi.org/10.3109/01913129109016242)

Received in final form 15 August 2019
Accepted 9 September 2019
Accepted Preprint published online 9 September 2019