An Overview of Autosomal Dominant Tumour Syndromes with Prominent Features in the Oral and Maxillofacial Region

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Abstract Several autosomal dominant inherited tumour syndromes demonstrate prominent features in the oral and maxillofacial region. Although multiple organ systems are frequently involved, the target organs more frequently affected are the skin (nevroid basal cell carcinoma syndrome, Brooke–Spiegler syndrome, Birt–Hogg–Dube syndrome and Muir–Torre syndrome), gastrointestinal tract (Peutz–Jegher syndrome and Gardner syndrome) or endocrine system (multiple endocrine neoplasia type 2b and hyperparathyroidism-jaw tumour syndrome). In some syndromes, the disease is multisystem with skin index lesions presenting in the head and neck (Cowden syndrome and tuberous sclerosis complex). The pertinent features of these syndromes are reviewed with a systems-based approach, emphasising their clinical impact and diagnosis.

Keywords Tumour syndrome · Oral · Maxillofacial

Introduction

Several autosomal dominant inherited tumour syndromes involve the oral and maxillofacial region. In a subset of the lesions in this region, the features are predictive of the

background genetic abnormalities. In most of these syndromes, the manifestations are most predominant in a single organ system such as the skin (nevroid basal cell carcinoma, Brooke–Spiegler, Birt–Hogg–Dube and Muir–Torre syndromes), gastrointestinal tract (Peutz–Jegher and Gardner syndromes) or endocrine system (multiple endocrine neoplasia type 2b, hyperparathyroidism-jaw tumour syndrome). However, in a minority of autosomal dominant tumour syndromes, there may be significant skin involvement but without any single predominating organ system (Cowden syndrome, tuberous sclerosis complex). Awareness and understanding of these syndromes among clinicians and pathologists caring for the face, jaws and mouth will facilitate earlier diagnosis and appropriate management. Here we review the key features of these syndromes, a summary of which is provided in Table 1.

Cowden Syndrome

The PTEN hamartoma tumour syndromes are a spectrum of tumour disorders driven by germline mutations of the tumour suppressor gene *PTEN* located at 10q22–23. Cowden syndrome is considered the prototypic example and gives rise to prominent manifestations in the oral and maxillofacial region. The precise diagnostic criteria of Cowden and PTEN hamartoma syndromes continues to evolve, as highlighted by a recent revision proposed by Pilarski et al. [1] and summarised in Table 2. The prevalence of Cowden syndrome has been estimated as 1/250,000 utilising data for the Dutch population [2].

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Table 1 Summary of the features of tumour syndromes with specific features in the oral and maxillofacial region

Syndrome	Head and neck index lesions	Major features in other systems
Cowden	Skin: Trichilemmomas Oral mucosa: Papillomatous papules	Breast, thyroid and endometrial carcinoma
Tuberous sclerosis complex	Skin: Angiofibromas; Fibrous plaques Teeth: Enamel pitting	Kidneys, Angiomyolipomas; Cysts Central nervous system: Tumours, Cortical dysplasias; Learning difficulties; Seizures
Nevoid basal cell carcinoma syndrome	Jaws: Odontogenic keratocysts Skin: Basal cell carcinomas	Ovarian fibroma Medulloblastoma
Brooke–Spiegler syndrome	Skin: Cyndromas; Trichoepitheliomas; Spiradenomas	None
Muir–Torre syndrome	Skin: Sebaceous carcinomas; Sebaceous adenomas	Colorectal, urothelial and endometrial carcinoma
Birt–Hogg–Dubé Syndrome	Skin: Fibrofolliculomas	Lungs: Cysts; Pneumothoraces Kidneys: Carcinomas
Peutz–Jeghers syndrome	Skin/mucosa: Pigmentation	Gastrointestinal polyps; Gastrointestinal carcinoma
Gardner Syndrome	Jaws: Osteomas; Odontomas; Supernumerary teeth	Colorectal adenocarcinoma
Multiple endocrine neoplasia 2B	Lips/oral mucosa: Mucosal neuromas	Pheochromocytomas Medullary thyroid carcinoma
Hyperparathyroidism–Jaw tumour syndrome	Jaws: Fibro-osseous lesions of the jaws	Parathyroid glands: Adenomas; Carcinomas Kidneys: Wilms tumour, Carcinomas; Cysts

Table 2 Proposed diagnostic criteria for *PTEN* hamartoma tumour syndrome [1]

Major criteria ^a	Minor criteria ^a
Breast cancer	Colon cancer
Endometrial carcinoma	Renal cell carcinoma
Follicular thyroid carcinoma	Papillary thyroid carcinoma
Three or more gastrointestinal hamartomas (e.g. ganglioneuromas) discounting hyperplastic polyps	Thyroid adenoma or multinodular goitre
Adult onset dysplastic gangliocytoma	Three or more lesions of oesophageal glycogenic acanthosis
Macrocephaly	Three or more lipomas
Macular pigmentation of the glans penis	Testicular lipomatosis
Three or more multiple trichilemmomas, acral keratoses, mucocutaneous neuromas or oral papillomatous papules	Vascular anomalies (including multiple intracranial developmental venous anomalies)
	Intellectual disability
	Autism spectrum

^aFor individual cases an operational diagnosis is made in the presence of 3 major criteria (one must include macrocephaly, adult onset dysplastic gangliocytoma, or gastrointestinal hamartomas); or two major and three minor criteria. Any two major criteria; or one major and two minor criteria; or 3 minor criteria are sufficient for an operational diagnosis in a family where one individual meets the clinical diagnostic criteria or has a *PTEN* mutation

Mutated Gene

The syndrome is caused by mutations in *PTEN* (*Phosphatase and tensin homolog*) gene [3]. The wild-type protein is a ubiquitously expressed dual-specificity phosphatase that acts as a tumour suppressor inhibiting the PI3K/Akt signalling pathway and mTOR activation.

Clinical Features

The typical mucocutaneous manifestations of Cowden syndrome are multiple facial trichilemmomas, acral keratoses and papillomatous lesions [1].

Multiple trichilemmomas (Fig. 1) develop on the face, typically in a perinasal and perioral distribution. These

Fig. 1 The photomicrograph shows a tricholemmoma populated by epithelial cells with clear to pale cytoplasm. There is a peripheral layer of columnar cells showing characteristic peripheral palisading of their nuclei associated with hyalinisation of the basement membrane. The lesion lies in continuity with the overlying hyperkeratotic epithelium

benign skin adnexal tumours possess a smooth or warty surface and range from 2 mm to more than 10 mm [4]. Acral keratosis presents as 2–3 mm skin coloured or tan papules on the palms and soles (and can resemble common warts) [5, 6].

Multiple papillomatous papules arise on the oral mucosa most commonly on the ventral tongue, lips, buccal mucosa, gingivae and palate [5, 7]. These flesh-coloured firm papules are 1–7 mm in diameter and their multiplicity can produce a cobblestone-like appearance [8, 9].

Internal features include the adult onset of a hamartoma of the cerebellum (dysplastic gangliocytoma or Lhermitte–Duclos disease), which has been strongly associated with Cowden syndrome [1]. Other features include adenomas and multinodular goitres of the thyroid, macrocephaly and gastrointestinal polyps [7].

The PTEN hamartoma of soft tissue was described in a series of 34 patients with Cowden or related PTEN syndrome. The lesions were characterised by a disorganized overgrowth of adipose tissue, dense fibrous tissue, myxoid fibrous tissue and vascular channels. Lymphoid follicles were also described and less frequently foci of metaplastic bone and hypertrophic nerves with a proliferation of periaxonal spindled cells. The maximum dimensions ranged from 1.2 to 25 cm and the majority manifested by the age of 15. The site was usually intramuscular and the majority occurred in the lower extremities. In 3 of the 34 cases described, the head and neck region was affected in sites including the masseter, lips, neck and face [10].

There is an established increased risk of cancers affecting the breast, thyroid and endometrium [1]. There is also evidence for an increased risk of renal and colonic

malignancy [1]. The risk of thyroid cancer is more than 70 times that of the general population [11]. Most cases are of papillary thyroid cancer, although follicular thyroid carcinoma is over-represented compared to trends in the general population [11].

Tuberous Sclerosis Complex

Tuberous sclerosis complex is a highly variable syndrome characterized by benign tumours in multiple organ systems. The term tuberous sclerosis derives from the appearance of congenital dysplastic lesions within the cerebrum. The most consistent manifestations of this complex are in the skin, central nervous system, heart, lungs and kidneys. Clinical diagnostic criteria are given in Table 3. Estimates of the prevalence vary, ranging for example from 1/11,000 to 1/27,000 within different UK communities [12, 13].

Mutated Genes

The most frequent mutations are in the *TSC2* (*Tuberous sclerosis-2*) gene with a smaller proportion of cases showing mutations in *TSC1* [14–16]. Inheritance is in an autosomal dominant manner, however, in 60% of cases there is no history of the condition in either parent [12]. The absence of a parental history of the condition is the result of frequent sporadic mutations as well germline mosaicism in at least some cases [17]. The wild-type *TSC1* and *TSC2* proteins are tumour suppressors that form a complex inhibiting mTOR [18].

Clinical Features

The variability of tuberous sclerosis complex reflects the differing effects of *TSC1* and *TSC2* mutations, variable expressivity and somatic mosaicism [12, 16, 17].

On the face and within the mouth, the majority of features are related to forms of fibrous proliferation. Multiple facial angiofibromas occur in the most cases particularly around the nose, appearing as firm skin coloured 2–3 mm telangiectatic papules [4, 16]. Facial angiofibromas are also described in multiple endocrine neoplasia 1 and Birt–Hogg–Dubé syndrome but are less prominent features. Fibrous plaques are common and are usually unilateral forehead lesions but can occur in other areas of the face and scalp [16, 19]. Multiple 1–2 mm flesh coloured mucosal fibromas occur on the oral mucosa particularly the gingivae [20]. The enamel surface of the teeth shows pitting in most cases, ranging from pinpoint to 3 mm in diameter [20]. Within the jaws, there are well-documented cases of fibrous proliferations often described as intra-osseous desmoplastic fibromas [21].

Table 3 Diagnostic criteria of tuberous sclerosis complex set in the 2012 International Tuberous Sclerosis Complex Consensus Statements [19]

Major features ^a	Minor features ^a
1. Three or more hypomelanotic macules (≥ 5 -mm)	1. “Confetti” skin lesions (numerous 1- to 3-mm hypopigmented macules scattered over the extremities)
2. Three or more angiofibromas or a fibrous cephalic plaque	2. Three or more enamel pits
3. Two or more ungual fibromas	3. Two or more oral fibromas
4. Shagreen patch	4. Retinal achromic patch
5. Multiple retinal hamartomas	5. Multiple renal cysts
6. Lymphangiomyomatosis	6. Non-renal hamartomas
7. Two or more angiomyolipomas	
8. Cardiac rhabdomyoma	
9. Cortical dysplasias: Includes tubers and cerebral white matter radial migration lines	
10. Subependymal nodules	
11. Subependymal giant cell astrocytoma	

^aTwo major features or one major feature with two or more minor features indicate a definite diagnosis. This is with the exception of a combination of lymphangiomyomatosis and angiomyolipomas without other features. Pathogenic *TSC1* or *TSC2* mutation in DNA from normal tissue is also sufficient for a definite diagnosis. A possible diagnosis can be made in the presence of one major feature or two or more minor features

Other dermatological features of the syndrome include hypomelanotic macules, ungual fibromas and Shagreen patches. Shagreen patches present as large plaques on the lower back that possess an uneven surface and result from subepidermal fibrosis. Hamartomas and achromatic patches of the retina are also features of tuberous sclerosis complex [16].

Lymphangiomyomatosis is seen in the lungs and rhabdomyoma in the heart [16, 22]. Within the renal system, the complex is associated with angiomyolipomas, multiple cysts and an increased risk of carcinoma [16, 23]. Angiomyolipomas are most common in the kidneys, but these and other similar tumours can occur at other sites. Renal disease is one of the leading causes of mortality among patients with tuberous sclerosis complex [24]. The other main cause of morbidity and mortality are manifestations within the central nervous system. These

include benign tumours and congenital cortical dysplasias such as the tuber-like lesions, for which the syndrome is named. Patients frequently show learning difficulties and suffer intractable seizures [16].

Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome is a tumour syndrome characterized by multiple basal cell carcinomas with an early age of onset together with the development of odontogenic keratocysts. Diagnostic criteria proposed by Kimonis et al. [25] are given in Table 4 [25]. Criteria were reviewed in 2005 at the first international conference, but a consensus was not reached [26]. Estimates of the prevalence range from 1/55,600 (England) to 1/256,000 (Italy) [27, 28].

Table 4 Proposed diagnostic criteria for nevoid basal cell carcinoma syndrome [25]

Major criteria ^a	Minor criteria ^a
1. Basal cell carcinomas: Three or more or one under the age of 20	1. Macrocephaly
2. Odontogenic keratocysts	2. Medulloblastoma
3. First degree relative with nevoid basal cell carcinoma syndrome	3. Cleft lip or palate, frontal bossing, hypertelorism
4. Bilamellar falx cerebri calcification	4. Ovarian fibroma
5. Bifid, fused or splayed ribs	5. Skeletal abnormalities: one shoulder blade sitting higher, pectus deformity, digital syndactyly
6. Three or more palmar or plantar pits	6. Radiological abnormalities: Bridging of the sella turcica, vertebral abnormalities, defects of the hands and feet

^aThe presence of two major or one major and two minor criteria was considered diagnostic

Mutated Gene

The classic syndrome is caused by mutations in the *PTCH1* (*Patched 1*) gene [29]. The wild-type receptor protein is a tumour suppressor that inhibits the Sonic Hedgehog signalling pathway [30]. Mutations in *PTCH2*, a homologue of *PTCH1*, have been described in a limited number of patients of Chinese and Japanese ethnicity [31, 32].

Clinical Features

The major features are basal cell carcinomas and odontogenic keratocyst. In one of the largest series, basal cell carcinomas occurred in 90% of Caucasians by the age of 35 [25]. Basal cell carcinomas numbered from 1 to more than 1000 with mean and median values of 62 and 8, respectively. The most common site was the face but lesions also developed on the trunk and limbs. Odontogenic keratocysts were present in more than 70% of patients, were usually multiple and occurred within the first two decades of life.

Palmar and plantar pits were seen in 87% of cases. The other main features included calcified falx cerebri and rib abnormalities. Minor or less frequent features included hypertelorism and a cleft lip or palate. Other minor features are detailed in Table 4. In addition to these, associations with the development of foetal rhabdomyomas and cardiac fibromas are reported [33, 34].

Odontogenic keratocysts occurring within this syndrome do not show features that are truly unique, but the lesions are more likely to be multiple and occur in the maxilla or in the anterior of the mandible rather than the angle. Syndromic odontogenic keratocysts have a greater propensity for showing epithelial budding, solid epithelial proliferations and satellite cysts within their wall (Fig. 2) [35].

Related Syndromes and Variants

Multiple hereditary infundibulocystic basal cell carcinoma syndrome is characterised by the development of multiple infundibulocystic basal cell carcinomas. These present mostly on the face but also the genitals and in the absence of other features of nevoid basal cell carcinoma syndrome [36, 37]. The syndrome is inherited in an autosomal dominant manner and has been associated with mutation in the *SUFU* (Suppressor of fused) gene, which acts downstream of *PTCH1* in the Hedgehog biochemical pathway. Mutation of *SUFU* in the absence of *PTCH1* mutations has been described in patients meeting the diagnostic criteria of classic nevoid basal cell carcinoma syndrome [38–40]. In the cases thus far described, patients did not develop odontogenic keratocysts and showed a greater risk of medulloblastoma and meningioma. It is possible that multiple hereditary infundibulocystic basal cell carcinoma syndrome and

Fig. 2 The first photomicrograph **a** shows a typical odontogenic keratocyst lined by stratified squamous epithelium with a thin wavy layer of parakeratin and a flat layer of palisaded basal cells. The second photomicrograph **b** shows an odontogenic keratocyst arising in a patient with nevoid basal cell carcinoma syndrome and known to possess a deletion on the long arm of chromosome 9 that included the *PTCH1* gene. This odontogenic keratocyst shows prominent budding of the basal cell layers

SUFU mutation associated nevoid basal cell carcinoma syndrome are phenotypic variants of a single syndrome.

Basal cell carcinomas are also a feature of several unrelated syndromes, which are beyond the scope of this text but should be considered in a differential diagnosis. These include Rombo syndrome, Bazex's syndrome and Xeroderma pigmentosum.

Brooke–Spiegler Syndrome

Brooke–Spiegler syndrome is characterised by multiple benign tumours of the skin appendages. The condition is very rare and typically affects the head and neck region. Accurate estimates of the syndrome frequency are not available.

Mutated Gene

The syndrome is caused by mutations in the *CYLD* gene (*Cylindromatosis*), which are inherited in an autosomal dominant fashion [41]. Wild-type *CYLD* is a

deubiquitinase and tumour suppressor that downregulates the transcription factor NF-kappaB [42].

Clinical Features

Brooke–Spiegler syndrome causes the development of multiple benign skin adnexal tumours including cylindromas, spiradenomas and trichoepitheliomas. The syndromes of multiple familial trichoepitheliomas and familial cylindromatosis are considered to lie on the phenotypic spectrum of Brooke–Spiegler syndrome [43].

Tumours are typically located in the head and neck region and manifest in late childhood or adolescence as smooth skin coloured papules or nodules. Cylindromas predominate on the scalp, while trichoepitheliomas occur on the face, particularly around the nose [44]. Tumours increase in size and number with age and carry a risk of malignant transformation [45].

Salivary basal cell adenomas are rarely reported in association with Brooke–Spiegler syndrome [46, 47]. These benign salivary neoplasms have the alternative designation of the dermal analogue tumour and show remarkable histological similarities to the dermal cylindroma.

Birt–Hogg–Dubé Syndrome

Birt–Hogg–Dubé syndrome is characterized by multiple cutaneous hamartomas, pulmonary cysts, spontaneous pneumothoraces and an increased risk of renal cancer. The syndrome is very rare and accurate estimates of its frequency are not available.

Mutated Genes

Mutations in the *FLCN* (*Folliculin*) gene cause the syndrome [48]. The function of *FLCN* is not yet fully characterised.

Clinical Features

The typical skin lesions of Birt–Hogg–Dubé syndrome are described as fibrofolliculomas, trichodiscomas and acrochordons. Acrochordons or skin tags are common among the general population and can be considered a non-specific feature. Fibrofolliculomas and trichodiscomas are benign hamartomas of the hair follicle that are now deemed to represent the same entity and can both be designated fibrofolliculomas [49] (Fig. 3). At least 90% of Birt–Hogg–Dubé cases show fibrofolliculomas appearing as multiple 1–5 mm white or skin coloured papules on the face, neck and upper trunk [50]. A similar proportion of patients show lung cysts on imaging, and these are associated with pneumothoraces

Fig. 3 The photomicrograph shows a fibrofolliculoma with the typical features of cords and anastomosing strands of epithelial cells lying within a fibromyxoid stroma

[51]. Renal carcinomas associated with the syndrome are frequently multiple and bilateral. The most common histological type is chromophobe renal cell carcinoma [52].

Muir–Torre Syndrome

Muir–Torre syndrome is the association of a dermal sebaceous tumour with internal malignancy and is a variant hereditary non-polyposis colorectal cancer (Lynch syndrome) [53]. Using data combined from Scotland, Finland and the USA, the prevalence of *MSH2* and *MLH1* mutations has been estimated to be 1/3139 among persons aged 15–74 [54].

Mutated Genes

The syndrome is caused by mutation of DNA mismatch repair genes (most commonly *MSH2*, with less frequent mutation of *MLH1* and *MSH6*) [55, 56].

Clinical Features

Sebaceous neoplasms including sebaceous carcinoma (Fig. 4), sebaceous adenomas and other benign sebaceous tumours are markers of Muir–Torre syndrome [53, 57]. Sebaceous hyperplasia has not been definitively linked with Muir–Torre syndrome [57, 58]. Occasional sebaceous gland hyperplasias have been reported associated with internal malignancy, likely reflecting the underlying frequency of this diagnosis within the general population [58]. The majority of sebaceous neoplasms occur on the head and neck, specifically the face and peri-ocular region. However, a higher proportion of sebaceous neoplasms on

Fig. 4 The photomicrograph shows a sebaceous carcinoma demonstrating basaloid cells and atypical sebaceous cells arranged in an infiltrative pattern

non-head and neck sites are associated with Muir–Torre syndrome [57].

Sebaceous adenomas and carcinomas range in size from a few millimetres to a few centimetres. Sebaceous adenomas present as smooth yellow papules and are sometimes lobular [4]. Sebaceous carcinomas present as skin-coloured to reddish or yellowish nodules that may be smooth or ulcerated. In the ocular region, sebaceous carcinomas can cause thickening of the eye lid and are frequently mistaken for inflammatory conditions such as conjunctivitis or a chalazion. A useful sign is the “tigroid appearance” of the conjunctiva resulting from yellow lipid streaks [59].

Cutaneous sebaceous tumours and internal malignancies present over a similar age range, with medians of 50 and 53 years respectively [60]. Muir–Torre syndrome is most commonly associated with colorectal carcinomas as well as urothelial carcinomas and carcinomas of the endometrium [53, 60, 61]. A recent case report found an association with a parotid sebaceous carcinoma, although a metastasis could not entirely be excluded [62].

The diagnosis of a sebaceous neoplasm should prompt assessment for mismatch repair gene mutation [58]. In the first instance, immunohistochemistry can be performed on the tumour biopsy to determine if production of mismatch repair proteins has been lost, but the genetic analysis should still be undertaken.

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome is a hereditary intestinal polyposis syndrome associated with mucocutaneous macules and an increased risk of internal malignancies. Estimates based on the Uruguayan population indicate that the condition affects 1/155,000 live births [63]. World Health Organization (WHO) [64] diagnostic criteria for Peutz–Jeghers are given in Table 5.

Mutated Gene

STK11 (*Serine/threonine kinase 11*) gene mutations cause the syndrome [65]. The wild-type protein is a tumour suppressor that functions in cellular processes including DNA methylation [66].

Clinical Features

Muco-cutaneous pigmentation and gastrointestinal hamartomatous polyps are the defining features of the syndrome. The hamartomatous polyps have a histologically distinct appearance and occur throughout the gastrointestinal tract, but are most frequent in the small bowel [64]. The polyps are frequently symptomatic causing intussusception and obstruction, torsion, infarction and bleeding. In one series, 68% of adults with Peutz–Jeghers syndrome had undergone a laparotomy for bowel obstruction by age 18 [67].

Pigmentation occurs at multiple sites with the lips and oral mucosa being the most consistently involved [63]. Other sites include the peri-ocular region, toes, hands and genitals [63]. The macules appear similar to freckles but are distinguished as freckles are sparse near the lips and do not involve the mucous membranes. Moreover, freckles wax and wane with sun exposure. Many reviews report that the pigmentation fades with age [68]. Pigmented macules on the skin and mucosa are seen in other syndromes such as the benign Laugier–Hunziker syndrome from which Peutz–Jeghers syndrome must be differentiated.

Peutz–Jeghers syndrome is associated with an increased risk of malignancy in the upper gastrointestinal tract, lower gastrointestinal tract as well as extra-gastrointestinal sites [69, 70]. Some large series have shown an increased risk of malignancy in the pancreas, gynecological tract and female

Table 5 WHO diagnostic criteria for Peutz–Jeghers [64]

1 ^a	Three or more histologically confirmed Peutz–Jeghers polyps
2 ^a	Any number of Peutz–Jeghers polyps with a family history of the syndrome
3 ^a	Characteristic prominent mucocutaneous pigmentation with a family history of the syndrome
4 ^a	Any number of Peutz–Jeghers polyps and characteristic prominent mucocutaneous pigmentation

^aThe meeting of criteria 1, 2, 3 or 4 is considered diagnostic.

Table 6 WHO diagnostic criteria for FAP [64]

1 ^a	100 or more colorectal polyps
2 ^a	<i>Adenomatous polyposis coli</i> gene germline mutation
3 ^a	Family history of FAP and at least one epidermoid cyst or osteoma or desmoid tumour

^aThe meeting of criteria 1, 2 or 3 is considered diagnostic

breast [69–72]. There is also an association with Sertoli cell neoplasia of the testes [73].

Gardner Syndrome

Gardner syndrome is a variant of familial adenomatous polyposis syndrome (FAP) in which the extra-colonic manifestations are more prominent. It is characterised by numerous colonic polyps, osteomas and various soft-tissue tumours [74, 75]. The frequency of Gardner syndrome is challenging to separate from that of classical FAP. Utilising data for the Dutch population, the annual incidence and prevalence of FAP have been estimated to be 1.9/1,000,000 (1990–1999) and 4.65/1,000,000 (1999) respectively [76]. The WHO [64] diagnostic criteria for FAP are given in Table 6.

Mutated Gene

The syndrome is a result of mutations in the *APC* (*Adenomatous polyposis coli*) gene [74]. The wild-type protein is a tumour suppressor with functions including negative regulation of beta-catenin [77].

Clinical Features

In classical FAP and Gardner syndrome, there is the development of more than 100 colorectal adenomas during the second decade of life [64].

Osteomas in the oral and maxillofacial region are typical of Gardner syndrome and have been found in more than 50% of patients with FAP [78] (Fig. 5). These benign tumours commonly develop in the paranasal sinuses, the mandible and maxilla. There is a less frequent but significant association with odontomas and supernumerary teeth [78]. Focal increases in bone density within the gnathic bones are also described [78]. All of these features can allow for an early diagnosis of the syndrome.

Hypertrophy of retinal pigment epithelium is very common in Gardner syndrome and results in a pigmented ocular fundus [79]. Patients also frequently show multiple epidermoid cysts, lipomas and tumours of fibrous tissue including the Gardner fibroma that shows distinct histological features [80, 81].

Fig. 5 The photomicrograph shows an osteoma excised from the body of the mandible in a case of Gardner syndrome/FAP. The osteoma is formed from lamellar bone together with fatty marrow

Colorectal adenocarcinoma develops in almost all patients without intervention [64]; there is also an increased risk of adenocarcinoma in the upper gastrointestinal tract [82]. Patients also carry a raised risk of hepatoblastoma, medulloblastoma and papillary thyroid carcinoma [83–85]. The cribriform-morular variant of papillary carcinoma has been particularly associated with FAP [86].

Multiple Endocrine Neoplasia 2B

Multiple endocrine neoplasia 2 (MEN2) is a syndrome associated with the development of medullary thyroid carcinoma. It is divided into MEN2A, MEN2B and familial medullary thyroid carcinoma. MEN2B is separated from MEN2A by the absence of primary hyperparathyroidism due to parathyroid hyperplasia and the presence of extra-endocrine features. Familial medullary thyroid carcinoma cases by definition develop medullary thyroid carcinoma only. The estimated total incidence of MEN2 is 1.25–7.5/10,000,000 per year and the prevalence is estimated to be 1/35,000 [87]. MEN2B is the least common MEN2 subtype and accurate estimates of its individual frequency are not available.

Mutated Gene

The definitive diagnosis of MEN2 is based almost entirely on the presence of germline *RET* (Rearranged during transfection) gene mutation [87]. MEN2B has been specifically linked to mutations affecting codon 918 [88]. The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase that activates several signalling cascades.

Clinical Features

MEN2B is associated with the development of pheochromocytomas, a feature also seen in MEN2A. The extra-endocrine features seen only in MEN2B include variable expression of a marfanoid build characterised by thin elongate limbs and muscle wasting, ganglioneuromatosis of the digestive tract, thickened corneal nerve fibres and mucosal neuromas [89–91].

Mucosal neuromas typically develop on the lips, anterior tongue and other oral sites. Also frequently affected are the conjunctiva, nasal mucosa and laryngeal mucosa [89]. The lesions appear as multiple 2–7 mm yellow to white sessile painless nodules [92] (Fig. 6). When in enough numbers, labial lesions give a “blubbery” appearance. Rare cases of mucosal neuromas are described outside of MEN2B [92, 93]. Mucosal neuromas are evident in many cases at birth and in the majority of cases within the first decade. Importantly, this precedes the development of pheochromocytomas and medullary thyroid carcinoma [89].

MEN2B-associated medullary thyroid carcinoma has an early onset and an aggressive course [94, 95]. In a North American cohort, the median age of thyroidectomy for MEN2B patients with medullary thyroid carcinoma was

Fig. 6 The photomicrograph shows a mucosal neuroma that was located on the tongue. There is a proliferation of small nerves within the papillary mucosa. Myxoid change is frequent and perineurium is prominently thickened

13.5 years (range 5–25.5) [95]. The British Thyroid Association advises thyroid surgery as early as possible and preferably before the age of one year [96].

Hyperparathyroidism-Jaw Tumour Syndrome

Hyperparathyroidism-Jaw tumour syndrome is characterised by parathyroid adenomas and parathyroid carcinoma with associated hyperparathyroidism together with fibro-osseous lesions of the jaws [97–99]. The incidence of this relatively recently described syndrome is still unknown.

Mutated Gene

CDC73 (*Cell Division Cycle Protein 73*) gene mutations are causal [100]. The encoded wild-type protein, parafibromin, is a tumour suppressor that exerts several effects including repression of the *c-Myc* proto-oncogene [101].

Clinical Features

Parathyroid adenomas with associated hyperparathyroidism develop at an earlier age than their sporadic counterparts [98]. The parathyroid adenomas are often solitary but can be multiple and show a tendency to recur [97, 98]. There is a significantly increased risk of parathyroid carcinoma [98].

Changes within the gnathic bones fall within the spectrum of fibro-osseous lesions. A cellular fibrous stroma is formed containing trabeculae of woven bone with variable osteoblast rimming and/or cementum-like deposits [98]. Both the mandible and maxilla can be involved and the lesions can be multiple. The jaw lesions are distinguished from the classical lytic “brown tumours” associated with hyperparathyroidism by their persistence following correction of hypercalcaemia and the lack of giant cells on histology [97].

Development of Wilms tumour of the kidney in association with the syndrome is well established [98]. Other associated renal lesions include benign cysts and papillary renal cell carcinomas [99]. Papillary thyroid carcinoma and pancreatic adenocarcinoma have also been described coincident with this syndrome [99].

Discussion

The early diagnosis of the above-described tumour syndromes will allow appropriate screening for and prophylactic or early stage care of associated malignancies. Application of clinical diagnostic criteria aids in the identification of syndromic patients. However, the

rarity of the syndromes has in most cases precluded the rigorous assessment of the predictive power of diagnostic criteria. The proposed diagnostic criteria should be used as a guide and not to exclude suspected cases from genetic counselling and mutation analysis. Assessment for the presence of many diagnostic features requires imaging and invasive techniques such as colonoscopy. An approach utilising index lesions in the oral and maxillofacial region may expedite appropriate genetic testing. The most important index lesions include multiple adnexal tumours, angiofibromas, multiple odontogenic keratocysts, odontomas, osteomas, mucosal neuromas and fibro-osseous lesions of the jaws.

Identification of the defined genetic mutation can be considered the gold standard for diagnosis, however, in many cases, the phenotype that develops is influenced by variable expressivity and incomplete penetrance. The penetrance of FAP and MEN2B is near complete [94, 102]. In contrast, hyperparathyroidism-jaw tumour syndrome has a low penetrance in at least some cohorts [103, 104]. As discussed above, the phenotype of patients with tuberous sclerosis complex is influenced by variable expressivity as well as somatic mosaicism and the differing impacts of mutations in two different genes [12, 16, 17].

In a significant subset of patients with the full clinical features of a syndrome, mutations in the known causative genes cannot be detected. For example, in a large cohort of patients with a definite diagnosis of tuberous sclerosis complex, no mutation could be identified in 29% of cases [16]. In some cases, this may be explained by mutations in genes other than those classically associated with a syndrome but producing similar features. This is exemplified by the identification of mutations in *succinate dehydrogenase subunits B* and *D* that are associated with a Cowden-like syndrome in patients who lack *PTEN* mutations. These *succinate dehydrogenase* mutations influence the same biochemical pathway as *PTEN* emphasising that these syndromes should be considered a continuous rather than discrete variable [105].

Further guidance on diagnostic criteria and management is provided by the National Comprehensive Cancer Network (USA). Patients benefit from appropriate surveillance and in some cases prophylactic surgery. The use of targeted or biological therapies is a developing area. Everolimus is an mTOR inhibitor that may be used in both the USA and the UK in the management of appropriate cases of tuberous sclerosis complex associated subependymal giant cell astrocytoma in adults and children, and tuberous sclerosis complex associated renal angiomyolipomas in adults. Targeted therapies in the management of other syndromes are the subject of clinical trials.

Conclusion

Although identification of the defined genetic mutation is the diagnostic gold standard of genetic syndromes, a high level of suspicion is needed to identify carriers of the mutations when index lesions are present. These index lesions in the oral and maxillofacial region include multiple adnexal tumours, angiofibromas, multiple odontogenic keratocysts, odontomas/osteomas, mucosal neuromas and fibro-osseous lesions of the jaws, which should lead to an early diagnosis of these syndromes when evaluated in the proper clinical context.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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