

An overview and update on bone lesion in craniofacial bones

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Abstract – 150 words.

Pathologists rarely see cases of bone tumours, which are rare entities, and their diagnosis is challenging. To achieve the correct diagnosis and for patients to be offered optimal treatment, it is critical that a multidisciplinary specialised team is involved. The last decade has seen exceptional advances in the molecular classification of bone tumours, which have not only made reaching diagnoses easier, but also makes the subspeciality an exciting area of research. Bone tumours are classified based on their histological features, irrespective of the anatomical site in which the tumour presents; however, not every tumour fits nicely into these categories as some share features. Bone tumours must be diagnosed in the context of the radiology, patient's symptoms, signs and family history. This article reviews key clinical, histologic features of bone tumours and highlights the recent advances made in understanding the pathology of bone lesions in the head and neck region.

Key words: Sarcoma, craniofacial bones, cancer, genetics, mosaicism

Introduction

Diagnosing bone tumours has been considered to be one of the most challenging areas in pathology. Much of this is because pathologists, both consultants and trainees, rarely see such cases. The reason is that musculoskeletal pathology is a niche area; malignant bone tumours are rare representing less than 1 % of all cancers but also because metabolic disorders involving the skeleton do not generally require a bone biopsy as the abnormalities can be assessed by non-invasive techniques. To ensure that sufficient experience is acquired by the multidisciplinary team involved in this area of clinical care there are only five centres in England commissioned to treat patients with bone tumours, and for pathologists to provide report on such cases. The reason for this is highlighted when you look at the numbers of malignant bone tumours in the UK. There are only about 120 new cases of osteosarcoma presenting in England annually. This compares with 55,000 new cases of breast cancers, 47,800 new cases of lung cancer, 42,300 new cases of colorectal cancer and 48,500 prostate cancers presenting annually.

Three of the five units commissioned to provide a bone tumour service in England are ‘stand-alone’ hospital sites which has advantages and disadvantages. It means that trainees are not exposed to the subject, the consequence of which is inadequate recruitment into this subspecialty. However, these stand-alone units have ‘punched above their weight’ in terms of research and development. Indeed, much of the advances in molecular classification of bone tumours in the last decade has been delivered from the UK. These advances have not only made the diagnosis of bone tumours easier, but it also makes the subspeciality an exciting area in which to work. The commitment to research and development in this area is reflected in that samples from more than 1000 patients were submitted to the 100,000 Genomes Project – this is likely to reflect that specialist units having a level of independence which allows them to be nimble in terms of changing practices rapidly as required. These samples submitted to the 100,000 Genomes Project for which whole genome sequencing are now available and provide an unmatched resource to be exploited for the improvement of patient care ¹.

Have you considered bone and soft tissue pathology as a subspecialty?

How to approach diagnosing bone tumours of the Head and Neck region

The approach is the same irrespective of the anatomical site in which the tumour presents but some tumours are more likely to occur in specific bones. This update cannot cover every entity and will focus on the most common entities and recent advances made in understanding the pathology of bone lesions in the head and neck region. For more in-depth reading see the WHO Classification of soft tissue and bone tumours ² and the Dorfman and Czerniak's Bone Tumors book ³ and recent reviews ^{4,5}. If you wish to perform continued education easily in this discipline you can access new bone and soft tissue tumours described every fortnight in our BoSTT App (<https://apps.apple.com/gb/app/bostt/id995198514>).

Is the lesion a tumour or?

- a. Could it be a metabolic disorder – such as
 - i. Hyperparathyroidism
 - ii. Related to malabsorption
 - iii. Related to renal disease
 - iv. Related to liver disease
 - v. Related to other endocrine abnormalities for example thyroid and pituitary disorders
 - vi. Phosphate dysregulation which can be inherited
- b. A reactive/reparative process
 - i. Trauma/fracture
 - ii. Infection
- c. Autoimmune
 - i. Sarcoidosis

Classification of tumours

In the first instance always consider if the tumour is really a bone tumour – these are rare: metastatic carcinoma, melanoma and lymphomas are considerably more common. Make sure you exclude these before signing out a diagnosis of sarcoma!

- Bone-forming
- Cartilage-forming tumours
- Osteoclast-rich tumours
- Fibro-osseous tumours

But not every tumour fits nicely into these groups as some share features

- Notochordal

Next question – if it is a tumour; is it?

- Benign, malignant – and if malignant is it a primary or metastatic disease?
- Is the disease familial, what is the germline alteration?
- Is the tumour part of a mosaic disorder, resulting from an early post zygotic genetic alteration – such as Ollier disease/Maffucci syndrome, and fibrous dysplasia?

Presenting signs and symptoms

Most bone tumours present with pain. However, in the head and neck region they may present as a lump, or a deformity/asymmetry and or with complaints related to the site involved particularly if they are large, such as painless swelling, facial asymmetry sinusitis, and nasal discharge secondary to nasal or paranasal sinus obstruction.

Bone tumours must be interpreted in the context of the radiology

1. Bone-forming tumours

Osteoma

Osteoid osteoma and osteoblastoma

Osteosarcoma

Osteoma

This is a benign, slow growing bone-forming tumour that arises on bone surfaces and rarely occurs outside the skull. It consists largely of mature, compact/cortical-type bone. When it occurs in the medullary cavity it is referred to as a bone island. In most cases they are asymptomatic but are excised if causing problems. Although rare in children, osteomas affect all age groups but are most commonly diagnosed in the fourth or fifth decades of life. Often incidental findings, the true incidence is not known but may be present in as many as 10 % of the population.

In most cases osteoma presents as a single lesion and the cause is unknown. However, as often the case when an individual has multiple lesions they can be associated with an autosomal dominant disorder. Gardner's syndrome is a subtype of familial adenomatous polyposis coli caused by alterations in the *APC* gene. Multiple bone islands/osteopoikilosis is an autosomal dominant disease caused by loss of function of the *LEMD3* gene.

The tumour removed surgically is a sliver of dense solid bone and histologically is composed of compact bone and or broad trabeculae of mature bone; vascularity is conspicuous in the latter and a haemangioma might be considered in the differential diagnosis.

Local recurrence is rare and malignant transformation is not reported.

Osteoid osteoma and osteoblastoma

These are benign bone tumours distinguished arbitrarily by their size, the cut off being 20 mm, with the osteoid osteoma being the smaller. Approximately 10–15 % of osteoblastoma arise in the bones of the craniofacial skeleton but otherwise occur most frequently in the posterior elements of the vertebrae. Osteoid osteoma rarely occurs in the craniofacial bones. Both tumour types present generally under the age of 30.

Osteoid osteoma is associated with severe intense pain, particularly at night, which responds extremely well to non-steroid anti-inflammatory drugs (NSAIDs). Interestingly this association with response to NSAIDs in osteoblastoma is generally not so noteworthy despite the two entities being driven by the same genetic alterations. The cause of the pain is considered to be related to the high levels of prostaglandin E2 and prostacyclin found in the nidus which contributes to local inflammation and vasodilation. Prostaglandins also induce bone formation, and this explains the perilesional sclerosis and also the response to non-steroid anti-inflammatory drugs. Rarely, individuals with osteoid osteoma and osteoblastoma present with marked fever, weight loss which is considered to be related to high levels of prostaglandins.

Histological features are shown in Figure 1. Identification of *FOS* (87 %) and *FOSB* (3 %) rearrangements in both osteoid osteomas and osteoblastomas demonstrate that these tumours are closely related. It is noteworthy that the mutant cell population is small compared to the total cell population of the tumour. *FOS* and *FOSB* rearrangements can be detected by FISH

but expression of FOS by immunohistochemistry is more commonly employed for diagnostic purposes. However, FOS is expressed occasionally in osteosarcomas, so it is best interpreted in a specialist unit in the context of the radiology ⁵. FOSB rearrangements are also seen in vascular tumours, namely pseudomyogenic haemangi endothelioma and epithelioid haemangioma. More recently homozygous deletions in the *NF2* gene have been reported in osteoblastomas, and these occur mutually exclusively with alterations in FOS ⁶.

Osteoid osteomas are removed by ‘burning’ or curettage whereas osteoblastomas are generally removed by *en bloc* excision. Neither tumour transforms to malignant disease but osteoblastomas can recur and may behave in a locally aggressive manner.

Osteosarcoma

Osteosarcoma is a malignant neoplasm of bone and is characterised by osteoid/ bone formation. Whereas most osteosarcomas in the long bones present in the second decade, they occur a decade later in the maxillofacial region. About 6 % of osteosarcomas occur in the craniofacial area where they most frequently affect the jaw bones.

The cause of most cases of osteosarcoma is unknown but this cancer occurs more commonly in individuals with cancer predisposition disorders including Li-Fraumeni syndrome (*TP53* autosomal dominant disorder), Retinoblastoma (*Rb* gene – autosomal dominant disorder), Rothmund-Thomson syndrome (autosomal recessive disorder; *RECQL4* gene), and Bloom syndrome (*BLM* gene) and Werner syndrome resulting in premature aging (*WRN* gene; autosomal recessive disorder). Osteosarcoma also may occur secondary to radiation therapy given some considerable time previously.

Pain and swelling represent the most common symptoms. Radiology demonstrates if the tumour is arising in the medullary cavity ‘centrally’ (in the bone) or on the bone surface ‘peripherally’ (on the bone). In many cases the tumour is large, destructive and expansile.

The histological features of osteosarcomas are highly variable and even within a tumour it can exhibit different patterns. This includes extensive bone and or cartilage deposition (Figure 2), fibroblastic overgrowth with little bone formation, and a telangiectatic picture and tumours with large numbers of osteoclasts. There can be extensive necrosis and mitotic

activity can be high. However, these features do not predict outcome. It is important to distinguish a high grade from a low-grade osteosarcoma.

Most osteosarcomas are high grade. Most low-grade tumours of the jaw bone represent parosteal osteosarcoma (Figure 2) characterised by *MDM2* amplification, readily assessed by FISH. However, transformation of a low grade parosteal osteosarcoma to a high-grade disease can occur; *MDM2* amplification is retained.

The treatment of choice is *en bloc* surgical excision and for high grade disease adjuvant chemotherapy or radiation therapy can be given.

The most important predictor of outcome at diagnosis is the presence or absence of metastases and the most reliable prognostic factor is the histological response to pre-operative chemotherapy.

2. Notochordal tumours – chordoma

Chordoma is a malignant neoplasm showing notochordal differentiation; it presents in axial skeleton and bones of the base of the skull and exceptionally in soft tissue. It occurs in 1 in 800,000 and rarely in the black African population. Although chordoma presents at any age, with occasional cases reported at birth, it presents in the cervical vertebrae and bones of the base of the skull most commonly in young people.

Chordoma is generally a slow-growing disease but because of the anatomical site it is difficult to remove fully; recurrence is common and the mean survival is 7 years. Metastases occur frequently.

The cause of this disease is not known but it is associated with a SNP rs2305089 in the *TBXT* (brachyury) gene; this SNP is common in the population at large but uncommon in the African population suggesting that it has a causative role in the development of the disease. However, the impact of this SNP on the pathogenesis of chordoma is unknown.

Chordoma is classified as conventional, chondroid, dedifferentiated and poorly differentiated. All tumours express TBXT and cytokeratins, except in the dedifferentiated component where expression of TBXT is lost with or without loss of cytokeratins. The poorly differentiated variant is a particularly aggressive disease and is classified on the basis of loss of INI1 protein expression brought about by genetic alterations in *SMARCB1* (Figure 3).

Its rarity not infrequently results in the diagnosis being overlooked by clinicians and pathologists. The histological features mimic chondrosarcomas, and metastatic carcinoma in particular.

3. Fibro-osseous lesions

Fibrous dysplasia

Fibrous dysplasia is a benign non-familial fibro-osseous condition presenting centrally in the medullary cavity of the bone. There are monostotic and polyostotic forms.

The disease in children may result in deformed bones but this is variable depending on the bones involved. Approximately 2 % of cases progress to osteosarcoma or chondrosarcoma and this occurs more commonly in polyostotic forms.

The presentation of fibrous dysplasia is highly variable; it can be picked up as an incidental finding particularly in adults. In children presentation with a fracture is not uncommon. Pain may also be a complaint and not easily explained. It is thought that this may be related to microfractures as fibrous dysplasia lesions may be poorly mineralised due to low levels of phosphate resulting from fibroblastic growth factor 23 being secreted by the lesional cells; this results in reduced reabsorption of phosphate in the renal tubules. About 10 % of patients with fibrous dysplasia are thought to have hypophosphataemia.

The same recurrent genetic alterations in *GNAS* causes both the monostotic and the polyostotic forms of the disease. The latter presents more commonly in children and more commonly affects the craniofacial bone. The polyostotic variant is explained by the occurrence of an early post-zygotic alteration. This accounts for the additional non-skeletal lesions including intramuscular myxoma (referred to as Mazabraud syndrome) and endocrine disorders presenting in these individuals. Endocrine abnormalities caused by the same *GNAS* mutations in endocrine glands in the setting of pigmented skin lesions is known as McCune

Albright syndrome. However even in the absence of the characteristic skin lesions an endocrine work up is recommended for all individuals with polyostotic fibrous dysplasia as it is not uncommon for the symptoms caused by abnormal endocrine function may be subtle and insidious.

The radiology exhibits a characteristic ‘ground glass’ appearance on x-ray. The lesions replace the bone marrow but may also protrude onto the surface – fibrous dysplasia protuberans.

The histological features are generally not difficult to interpret but on occasions it may be difficult to distinguish from a low grade central osteosarcoma. Mitotic figures are rare but small numbers may be seen in children (Figure 4). Detection of the characteristic *GNAS* mutation is helpful in reaching a diagnosis. In contrast, about 20 % of low grade central osteosarcomas harbour *MDM2* amplification, which can be readily assessed by FISH; these alterations are mutually exclusive.

The disease may be managed by ‘watch and wait’ approach or surgical intervention may be required – usually curettage. The impact on patients’ lives is determined on the extent, the bones involved and the age of presentation.

4. Osteoclast-rich lesions

Osteoclast-rich lesions represent a diverse range of pathologies as listed below. The histological features can be indistinguishable, highlighting the importance of thinking as a clinician and about disease in patients and not just looking down the microscope!

Central giant cell granuloma –consider germline conditions such as Cherubism, Noonan Syndrome and Neurofibromatosis Type 1

Tenosynovial giant cell tumour – a neoplastic process

Giant cell tumour of bone - a neoplastic process

Aneurysmal bone cyst - a neoplastic process

Secondary aneurysmal cyst formation – a reactive process

Hyperparathyroidism – metabolic condition assessed in the first instance by assessing calcium and phosphate levels

Chondroblastoma – discussed under cartilaginous tumours

Histology of osteoclast-rich tumours

The features of any of the above lesion can be highly variable within and between tumours and can be indistinguishable from one another (Figure 5, 6, 7, 8).

Central giant cell granuloma of the jaw

A benign intraosseous non-neoplastic lesion occurring most commonly in the anterior mandible and often crossing the midline which is likely to occur before age 30 presenting as a painless swelling; in the larger more aggressive forms it can displace teeth and has a high incidence of recurrence.

The cause of central giant cell granuloma of the jaw is a descriptive term and represents a number of different pathologies including a rare manifestation of Noonan syndrome with or without multiple lentigines (previously Leopard syndrome), Neurofibromatosis type 1 (NF1), Jaffe-Campanacci syndrome characterised by multiple non-ossifying fibromas, café-au-lait macules and giant cell granulomas of the jaw, and craniofacial cutaneous syndrome. Noonan syndrome and NF1 represent the most common germline alterations occurring in approximately 1 in 2,500 and 3000 of the population. Noonan syndrome, an autosomal dominant trait, is caused by alterations in *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, and *BRAF* genes and characterized by a range of features but individuals may also be asymptomatic. The most common germline alterations involve *PTPN11* (approximately 50 %) of cases.

Treatment is determined by severity of features and may involve enucleation and curettage and ‘*en bloc*’ resection might be required.

Cherubism

An autosomal dominant condition restricted to the mandible other than cervical lymphadenopathy. Individuals present by the age of 6 years. Radiologically there is a symmetric bilateral enlargement of the mandible and maxilla, which may cause respiratory and speech problems, impaired vision and hearing, dysphagia. There may be displacement of the teeth. This is in contrast to osteoclast-rich lesions in Noonan syndrome and NF1 which are non-symmetric lesions and generally present in the teenage years or later. Furthermore, Noonan syndrome and NF1 are multisystem diseases.

Penetrance of Cherubism is incomplete and the severity of the deformity is highly variable. The enlargement of the jaw stabilises at puberty and may regress almost fully but complete resolution does not usually occur in severely affected individuals.

Cherubism is caused by a gain of function mutation in *SH3BP2* gene that is part of a signalling pathway that activates NFAT – a transcription factor implicated in osteoclastogenesis.

Surgical treatment may be considered post-puberty if spontaneous regression is incomplete.

Giant cell tumour of bone

A locally aggressive primary bone tumour rarely occurring in the immature skeleton in the subarticular zone, defined by the near universal (96 %) pathognomonic *H3-3A* G34 mutation, the vast majority represented by G34W for which there is an excellent antibody, and rarely by G34L (Figure 5). Due to this recent discovery it is now possible to state that the presence of giant cell tumour of in the craniofacial bones is exceptional^{5,7}.

Aneurysmal bone cyst

There are two types of aneurysmal bone cysts (ABC) (Figure 6). The primary variant is a benign, blood-filled cysts located in bone and can have osteoclast-rich areas. They are characterised by a *USP6* rearrangement in about 75 % of cases. Secondary ABC do not harbour this genetic alteration and occur as a reactive component of a number of other bone tumours, most of which are benign many of which can be classified on the basis of other genetic alterations including giant cell tumour of bone, fibrous dysplasia, osteoblastoma and chondroblastoma. *USP6* rearrangements also occur in about 90 % of nodular fasciitis and in myositis ossificans.

Intralesional curettage and bone grafting are the traditional operative treatments. There is no evidence that they transform to malignant disease.

Tenosynovial giant cell tumour

A giant cell-rich tumour that occurs in the synovium of tendon sheaths, bursa and joints and in the craniofacial bone it occurs most commonly in the temporo-mandibular joint of the jaw

of adults. It is caused by a structural alteration of the macrophage colony-stimulating factor (*CSF1*) gene resulting in increased expression of the protein, which is essential for osteoclast formation. The number of the mutated tumour cells is sparse and therefore FISH is not used as a diagnostic test.

The tumour has a characteristic lobulated tan greasy appearance. The histological features are seen in Figure 7. As chondroid metaplasia may occur in tenosynovial giant cell tumour, the differential diagnoses include synovial chondromatosis and soft tissue chondroma (described in next section and Figure 8).

Surgical excision is the common treatment but local recurrences are common and if lesions are difficult to excise and cause debilitating function there is evidence that the disease can be controlled tyrosine kinase inhibitors such as Emactuzumab and Turalio (pexidartinib). Malignant change is rare.

5. Cartilage-forming tumours

Conventional cartilaginous tumours, particularly enchondromas, osteochondromas and chondrosarcomas are exceptionally rare in the jaw and therefore the focus will be on the common entities and their mimics.

Benign: synovial chondromatosis, chondroblastoma and chondromyxoid fibroma

Malignant: mesenchymal chondrosarcoma

Synovial chondromatosis

A benign locally aggressive cartilaginous tumour composed of multiple hyaline cartilage nodules occurring in subsynovial joint tissue. It is characterised by *FNI – ACVR2A* fusion genes.

The tumours have a characteristic appearance (Figure 8). Similar features are seen in soft tissue chondroma but these harbour a *FNI* fusion gene with *FGFR1* and *FGFR2*.

Surgery is the treatment of choice. Recurrence is not uncommon, and malignant transformation is rare.

Chondroblastoma

Chondroblastoma is a benign tumour presenting most commonly in the first two decades of life but can occur later. Following the identification of the presence of H3-3B K36M mutation being pathognomic of chondroblastomas it can now be stated that this tumour very rarely occurs in craniofacial bones^{2,8}. The histological features can be quite mixed and are shown in Figure 9. Immunohistochemistry allows detected of the K36M mutation (Figure 9).

Treatment is by generally by curettage. Local recurrence may occur. Malignant transformation is not reported.

Chondromyxofibroma

Chondromyxoid fibroma is a benign cartilaginous bone tumour composed of lobules of chondroid and myxoid matrix formed by spindle or stellate shaped cells. It represents only about 2 % of all benign bone tumours so it is rarely seen in the maxillofacial region. Chondromyxoid fibroma presents mainly in the second and third decades but it has been reported to occur as late as 70 years old.

Figure 10 shows the histological features. Virtually all chondromyxoid fibroma harbour a recurrent *GRM1* fusion gene. However, the complexity of the structural rearrangement makes it difficult to be assessed by FISH and therefore there is currently no easy access to this as a diagnostic test.

Curettage is the standard treatment. Some cases recur but malignant transformation has not been reported.

Mesenchymal chondrosarcoma

Mesenchymal chondrosarcoma, a high-grade, biphasic tumour exhibiting primitive small cells and chondro-osseous deposition. It occurs in both bone and soft tissue but most bone lesions present in the craniofacial bones. It also occurs in the meninges. It peaks in the second and third decades.

It is characterised by a structural alteration resulting in fusion of *HEY1* and *NCOA2* which can be detected by FISH.

Figure 11 exhibits the histological features. The biphasic appearance and its rarity makes this a challenging diagnosis. Surgery with or without adjuvant therapy is standard of care treatment. Even with optimal therapy, relapse may occur after several years.

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MULTIPLE CHOICE QUESTIONS

1. The demographic data for a group of patients diagnosed with a primary bone lesion is analysed. Which of the following bone tumour most commonly occurs in males?

- A - Aneurysmal bone cyst
- B - Osteosarcoma
- C - Chondrosarcoma
- D - Osteblastoma
- E - Osteoid osteoma

Answer is A – Osteosarcoma

2. Which of the following is associated with high risk of osteosarcoma?

- A - Germline mutation of *TP53*
- B - Mutation on chromosome 8 resulting in fusion of *HEY1* and *NCOA2*
- C – Mutation in *IDH1*
- D – Mutation in *USP6*
- E – Mutation in *SH3BP2*

Answer is A - Germline mutation of *TP53*

3. Which one of the following statements about Mesenchymal Chondrosarcoma is false?

- A- Usually occurs within the first to fourth decades of life
- B- It is a rare, malignant form of chondrosarcoma
- C- Displays a predilection for the femur, spine, ribs, maxilla, mandible and pelvis
- D- It often appears indistinguishable to a central chondrosarcoma with characteristic chondroid calcification
- E- Recurrence is rare and metastases happen later and less frequently compared to central chondrosarcoma

Answer is E - Recurrence is rare and metastases happen later and less frequently compared to central chondrosarcomas.

Figure Legends

Figure 1. Osteoid osteoma and osteoblastoma. A lower power view shows interconnecting trabeculae of woven bone 'blue' which merges imperceptibly with the non-lesional bone at the periphery of the lesion (a). The dense 'blue' bone between the arrows represents the central nidus which is more conspicuous in the osteoid osteoma (b). A 'busy' arrangement of cells but on close inspection this represents a complex network of vascular channels (stars); plump osteoblasts line the trabecular (arrows) and osteoclasts are highlighted (magnified in circles) (c). There are very few mitotic figures and necrosis is not a feature. Tumour cells lining the bony trabeculae are immunoreactive for cFOS (d).

Figure 2. Osteosarcoma. High grade osteosarcoma exhibiting mitotic activity and irregular deposition of bone in an atypical fibroblastic population (a) and chondroblastic differentiation (b). Parosteal osteosarcoma is a low grade surface osteosarcoma characterised by *MDM2* amplification (not shown). There is often a cartilage cap (c) so the differential diagnoses include a chondroblastic osteosarcoma and osteochondroma both of which rarely occur in the gnathic bones. The majority of the tumour is composed of irregular cellular fascicles running parallel to woven bone trabeculae deposited by the tumour cells (d) which show limited nuclear atypia (e) and can be mistaken for fibrous dysplasia. However mutually exclusive molecular events can resolve this challenge (see relevant sections of text). Hence radiology is important for the interpretation of such lesions.

Figure 3. Chordoma. Typical features of different chordoma variants: conventional chordoma with a lobulated appearance with variable amounts of extracellular matrix: the cells have bubbly cytoplasm and low mitotic activity (a); dedifferentiated (b); chondroid (c); poorly differentiated (d) with loss of *INI1* (not shown).

Figure 4. Fibrous dysplasia. Irregular trabeculae of woven bone (seen on birefringent light microscopy) which are not lined by osteoblasts but rather merge with the surrounding bland spindle cells which replace the bone marrow (a). Mitotic figures and necrosis are not seen (a). Uncommonly, cartilaginous differentiation is seen (b).

Figure 5. Osteoclast-rich lesions. A largely spindle cell lesion with a storiform pattern and only scattered osteoclasts (enlarged in circle) (a) more commonly seen in peripheral giant cell granuloma. The other end of the spectrum is represented in (b), a picture most commonly seen in giant cell tumour of bone, confirmed by the expression of H3-3 G34W (c), although about 6% of giant cell tumour harbours a G34L mutation not detected by the antibody. Aneurysmal cyst formation with H3F3 G34W immunoreactivity (not shown) and not harbouring the characteristic *USP6* rearrangement in primary aneurysm bone cyst (d).

Figure 6. Primary aneurysmal bone cyst. A cystic fibrous lesion with extensive 'blue bone' which harbours a *USP6* rearrangement (not shown) (a) and an adjacent area with osteoclast condensation (b).

Figure 7. Tenosynovial giant cell tumour. A spindle cell tumour in which various numbers of osteoclasts are embedded. The spindle cells which harbour the mutation show no atypia but can be mitotically active (a). Foamy macrophages and haemosiderin may also be features. Chondroid metaplasia (b) is particularly common in the jaw raising the possibility of a cartilaginous tumour and particularly chondroblastoma and synovial chondromatosis (see Figure 8).

Figure 8. Synovial chondromatosis. Hyaline cartilaginous nodules partly calcified (a) with lack of cellular atypia and mitotic activity (b).

Figure 9. Chondroblastoma. A biphasic tumour composed of a cellular component in which areas of cartilage deposition exhibiting a pink osseous hue are found. The cellular component is composed of sheets of chondroblasts without atypia and very low numbers of mitotic figures. A variable number of osteoclasts are present (enlarged in circles) (a) and when are highly conspicuous it could be mistaken for a giant cell tumour of bone (b). Small chondrocyte-like cells are embedded with focal pericellular 'chicken wire' calcification (arrows) (a, c). The tumour cells express H3F3 K36M; note the nuclear expression (d).

Figure 10. Chondromyxoid fibroma. Lobules of chondro-myxoid matrix surrounded by fibrous bands (a) where osteoclasts tend to accumulate (not shown). Embedded in the matrix are small spindle cells without mitotic activity (b). However, atypia can be marked but these cells are not mitotically active and have abundant cytoplasm (a low nuclear cytoplasm ratio) – not shown.

Figure 11. Mesenchymal chondrosarcoma. A biphasic tumour; the chondro-osseous component (a) showing abundant deposition (star) alongside primitive cells with a 'small round blue cell' appearance (b). The components visualised together facilitates the diagnosis.