Tumours of the Ear

Tumours are unusual in the ear. In the external ear most of the neoplasms are those of the covering skin. Only the ceruminous glands are peculiar to the external ear, but ceruminous tumours are rare. The underlying bone contributes some swellings and neoplasms to this area. The most common tumour in the middle ear is the adenoma, which arises from low-mitotic cuboidal epithelium that may become neoplastic. The inner ear is composed of a specific inert bone, a virtually non-mitotic sensory area and nerves. Tumours that are derived from Schwann cells are the only frequent neoplasms of the inner ear, indeed of the whole temporal bone.

Diagnosis of ear tumours presents a peculiar difficulty in that the whole structure is often encased in dense bone. Although modern imaging techniques have helped greatly to identify tumours and tumour-like lesions of the ear, there is still a need for autopsy studies in this area.
<table>
<thead>
<tr>
<th>Tumours of the external ear</th>
<th>Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (<a href="http://snomed.org">http://snomed.org</a>). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.</th>
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<tr>
<td><strong>Benign tumours of ceruminous glands</strong></td>
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<tr>
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<td>Papillary tumours</td>
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<td>Aggressive papillary tumour</td>
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<td>Schneiderian papilloma</td>
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<tr>
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<tr>
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<tr>
<td>Osteoma and exostosis 9180/0</td>
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<tr>
<td>Angiolymphoid hyperplasia with eosinophilia 9125/0</td>
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<td><strong>Tumours of the middle ear</strong></td>
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<td><strong>Papillary tumours</strong></td>
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<tr>
<td><strong>Tumours of the inner ear</strong></td>
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<td>Langerhans cell histiocytosis 9751/1</td>
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</tbody>
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1 Morphology code of the International Classification of Diseases for Oncology (ICD-O) (821) and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for borderline or uncertain behaviour.
Ceruminous gland neoplasms of external auditory canal and cylindroma

Definition
External ear neoplasms derived from ceruminous glands are very uncommon and can be benign or malignant. Only the adenoma (ceruminoma) can be categorized as being derived specifically from ceruminous glands. Syringocystadenoma papilliferum and adenoid cystic carcinoma arising in this region can sometimes manifest an origin from ceruminous glands. These tumours are either benign or malignant.

Localization
The expected site of origin is in the superficial part of the external canal.

Clinical features
The symptoms of this lesion, like other external ear canal lesions, are conductive hearing loss and discharge. Pain and facial nerve palsy are clinical predictors of malignancy.

Epidemiology
The benign and malignant tumours occur with equal frequency in men and women with a mean age of 49 years (range 26-89 years) [569,1478,1589].

Adenoma of ceruminous glands
ICD-O code 8420/0

Macroscopy
Gross appearances are those of a non-ulcerating superficial grey mass up to 4 cm in diameter, which is covered by skin.

Histopathology
Microscopically this neoplasm lacks a capsule. It is composed of regular oxyphil glands often with intraluminal projections. The glandular epithelium is bilayered. The outer myoepithelial layer may not be obvious in all parts of the neoplasm. In some ceruminomas, acid-fast fluorescent ceroid pigment may be found which is similar to that seen in normal ceruminal glands [2778].

Electron microscopy. One case of ceruminous gland adenoma showed apocrine caps, microvilli, cell junctions, secretory granules, vacuoles, lipid droplets and siderosomes, the characteristic ultrastructural features of apocrine glands [2260].

Chondroid syringoma
Definition
Benign tumour similar to the pleomorphic adenoma of salivary glands.

ICD-O code 8940/0

Synonym
Pleomorphic adenoma or mixed tumour.

Histopathology
Cartilage, myoepithelial and adenomatous structures are features of this neoplasm.

Syringocystadenoma papilliferum
Definition
Benign adnexal tumour with features similar to those seen at other sites.

Fig. 7.1 Ceruminous adenoma. Keratinized squamous epithelium overlies a circumscribed but unencapsulated neoplastic proliferation of ceruminous glands. Note glandular and small cystic profiles.

Fig. 7.2 Ceruminous adenoma. Stratification of the nuclei with moderate nuclear pleomorphism and a mitotic figure (upper left); Abundant eosinophilic-granular cytoplasm in the luminal cells which show focal decapitation secretion (upper right); glandular structures separated by fibrous connective tissue (lower left); inner luminal secretory cells subtended by basal myoepithelial cells demonstrate the dual cell population (lower right).
ICD-O code 8406/0

Synonym Hidradenoma papilliferum

Epidemiology and localization
Syringocystadenoma papilliferum is seen in children or young adults usually on the scalp or face. Occasionally it occurs in the ear canal.

Histopathology
Cystic invagination from surface epithelium. Projecting into the lumen are papillae covered by bilayered apocrine glandular epithelium which may show decapitation secretion typical of ceruminous glands.

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ICD-O code 8200/0

Synonym Turban tumour

Localization
In the external ear the lesion may be present on the pinna or in the external canal. In these situations it may be part of a multiple “turban tumour” presentation of this neoplasm on the scalp.

Histopathology
It is composed histologically of rounded masses of small, darkly staining cells which fit together in a jigsaw-like pattern and are surrounded by pink-staining hyaline material. Extracellular hyaline globules are often present in the cellular masses. Larger cells with vesicular nuclei are also seen. In contrast to primary adenoid cystic carcinoma, cylindroma in the external canal does not have a cribriform structure, but does have larger cells with vesicular nuclei.

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Fig. 7.3 Ceruminous adenoma. A Yellow-brown “ceroid” lipofuscin-like material is seen in the cytoplasm of ceruminous cells, a feature seen in modified ceruminous sweat glands and in ceruminous adenomas. B Glandular structures show ceruminous decapitation secretion in the luminal cells subtended by a prominent, well-defined myoepithelial cell layer (left). The myoepithelial cell nuclei are accentuated with a p63 immunoreaction (right). C Differential immunohistochemical staining highlights the luminal cells (CK7, left) while CK5/6 accentuated the basal cells (right).

Fig. 7.4 Syringocystadenoma papilliferum of external ear canal. Note papillae lined by bilayered glandular epithelium projecting into a cystic lumen. There is also a prominent epidermoid cyst.

Fig. 7.5 Cylindroma of pinna with multiple spherical lesions on pinna, face and temporal region. From L. Michaels & H. Helquist (1711).

Fig. 7.6 Cylindroma of pinna showing jigsaw-like pattern of cell groups, surrounded by hyaline basement membranes.
Malignant tumours of ceruminous glands

Definition
An infiltrating neoplasm derived from ceruminous glands.

ICD-O codes
- Adenocarcinoma 8420/3
- Adenoid cystic carcinoma 8200/3
- Mucoepidermoid carcinoma 8430/3

Localization
Superficial part of the external ear canal. Origin from the adjacent parotid salivary gland should be excluded.

Histopathology

Low and high-grade adenocarcinoma
These neoplasms possess a glandular structure with evidence of apocrine differentiation and infiltration. Low-grade tumours show loss of a myoepithelial layer and infiltration. The cells of high-grade tumours are markedly atypical with increased mitotic activity and widespread invasion.

Adenoid cystic carcinoma
The microscopic features of these tumours are indistinguishable from those arising in salivary glands. They characteristically widely infiltrate adjacent tissues and invade nerve sheaths.

Mucoepidermoid carcinoma
The tumours arising in this location are usually low-grade and the microscopic features are similar to those arising in salivary glands.

Prognosis and predictive factors
Recurrence often complicates surgical removal of high-grade tumours. Death due to involvement of local vital structures and metastases has been reported. Relentless, although often delayed recurrence and eventual bloodstream metastasis, particularly to the lungs is likewise a feature of adenoid cystic carcinoma.
Squamous cell carcinoma of the external ear

**Definition**
This malignant tumour of stratified squamous epithelium arises from the normal epidermal covering of the external canal of the pinna.

**ICD-O code**
8070/3

**Synonyms**
Epidermoid carcinoma, squamous carcinoma

**Epidemiology**
The average age at diagnosis is 65-70 years for the pinna lesions and there is a male predominance. The age at presentation is 52-55 years for the external canal tumours which show a female predominance (1226).

**Etiology**
Actinic overexposure and frostbite have been suggested as causes of the pinna lesion. The canal tumours have been linked with the same tumour type in the middle ear as possibly resulting from prolonged chronic inflammation. It is possible, however, that the clinical impression of chronic inflammation has been mistaken, the patients’ symptoms being the result of an occult squamous cell carcinoma.

**Localization**
The majority of squamous cell carcinomas of the external ear arise on the pinna; a lesser number arise in the external canal. The external ear sites of involvement in the pinna in a study of 52 patients are shown in Table 7.1. Rarely there is bilateral external ear involvement (2807).

**Clinical features**
The pinna lesions being in an exposed position are identified early. A serious problem with the canal lesions is the delay in diagnosis because of the minimal symptoms that may be present. Pain, hearing loss and drainage of blood or pus are the main features in that group. A plaque-like or even polyloid mass may be felt or even seen.

**Macroscopy**
Squamous cell carcinomas arising on the pinna grossly resemble those seen elsewhere on the skin. The appearances of the canal lesions are those of a mass, sometimes warty, occluding the lumen and invading deeply into the surrounding tissues. There may be dissolution of the tympanic membrane with invasion of the middle ear. Occasionally, the well-differentiated lesions may not be detected clinically until well advanced.

**Tumour spread and staging**
The TNM staging for skin does not seem applicable at this site because of the presence of cartilage invasion.

**Histopathology**
Epidermoid carcinoma of the external ear usually shows significant degrees of keratinization. Those showing a spindle cell morphology must be differentiated from melanomas and soft tissue tumours. In the cases with a canal origin evidence of origin from canal epidermis is usually present. In cases arising deeply within the ear canal there is usually a concomitant origin from middle ear epithelium and dissolution of the tympanic membrane. The neoplasm may be so well differentiated that it can be confused with a papilloma. The association of such a neoplasm with marked desmoplasia may further delay the correct diagnosis. Verrucous carcinoma has been seen in the external ear (2456).

**Precursor lesions**
Actinic keratosis may precede squamous cell carcinoma.

**Prognosis and predictive factors**
Squamous cell carcinoma of the pinna is an aggressive disease with a high propensity for local recurrence. Tumours confined to the external ear usually have a good outlook after surgical therapy. The outcome of the disease following surgical excision is related to the clinical stage at presentation, the higher the stage the worse the outcome (1915). Metastatic spread of squamous carcinoma of the pinna and external auditory meatus to lymph nodes is unusual. Lesions arising in the canal have a worse prognosis because of the late diagnosis and invasion of adjacent structures.

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**Table 7.1** Sites of involvement of squamous cell carcinoma of the pinna in 52 patients (2336).

<table>
<thead>
<tr>
<th>Site</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helix</td>
<td>27</td>
</tr>
<tr>
<td>Posterior auricle</td>
<td>11</td>
</tr>
<tr>
<td>Antihelix</td>
<td>6</td>
</tr>
<tr>
<td>Triangular fossa</td>
<td>3</td>
</tr>
<tr>
<td>Concha</td>
<td>3</td>
</tr>
<tr>
<td>Lobule</td>
<td>2</td>
</tr>
</tbody>
</table>

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**Fig. 7.8** Squamous cell carcinoma of the pinna forming a large mass with central ulceration.
Embryonal rhabdomyosarcoma

Rhabdomyosarcoma and its variants have been comprehensively discussed in the WHO Classification of Tumours of Soft Tissue and Bone [775]. This section focuses on its occurrence as a primary tumour in the external ear canal.

**Definition**
A primitive malignant tumour with phenotypic and biological features of embryonic skeletal muscle.

**ICD-O code**
8900/3

**Synonyms**
Myosarcoma, embryonal sarcoma, botryoid sarcoma.

**Epidemiology**
Rhabdomyosarcoma is rare in any part of the body. There is a distinct group arising in the head and neck of children, often very young, with a predilection for the palate, middle ear and orbit.

**Localization**
Most of the tumours arise in the middle ear with extension into the external canal as an “aural polyp”.

**Clinical features**
Embryonal rhabdomyosarcoma should be excluded in any child presenting with a polyp in the external ear canal. Advanced cases may present with aural discharge, facial weakness and swelling in the region of the ear [1116]. Extensive destruction of the bone at the base of the skull, especially the petrous bone has been described.

**Histopathology**
Only the embryonal subtype of rhabdomyosarcoma is recognized as occurring at this site. The characteristics of this polypoid tumour are those of rhabdomyoblasts and primitive mesenchymal cells showing a variable degree of skeletal muscle differentiation loosely arranged but with condensation beneath the epithelium (cambium layer). Yolk sac tumour has been described as a polypoid tumour presenting in the external ear canal. However, this is histologically distinct, being composed of small round blue cells arranged in a vacuolated pattern with formation of Schiller-Duval bodies and expressing alpha fetoprotein [833]. A detailed description of embryonal rhabdomyosarcoma including immunophenotype is given in the WHO Classification of Tumours of Soft Tissue and Bone [775].

**Histogenesis**
Although it is suggested that this tumour arises from striated muscle fibres in the middle ear, it seems more likely that the origin is from undifferentiated mesenchymal cells.

**Genetics**
Mutations in a region mapped to the short arm of chromosome 11 (11p15) have been associated with most embryonal rhabdomyosarcomas. Several genes have been mapped to this site. Complex structural and numerical chromosomal rearrangements have been associated with embryonal rhabdomyosarcoma. These are discussed in detail in the WHO Bone and Soft tissue book.

**Prognosis and predictive factors**
Modern chemotherapeutic schedules have dramatically improved the outcome for children with this tumour.

---

Fig. 7.9 Ear rhabdomyosarcoma. A A central area of necrosis is surrounded by “primitive cells” with a very high nuclear to cytoplasmic ratio. The neoplasm is separated from the surface. B This polypoid tumour has a "Grenz-Zone" between the neoplastic cells and the mucosal surface. The malignant cells have abundant eosinophilic cytoplasm.
Fibrous dysplasia

Definition
Fibrous dysplasia (FD) is a benign localised intramedullary proliferation of trabecular woven bone admixed with fibrous tissue. It may be monostotic, involving one bone or polyostotic involving several bones.

Synonyms
Benign fibro-osseous lesion.

Epidemiology
FD affects children and adults and there is no geographical, or racial predilection. The monostotic form affects both sexes equally; the polyostotic form is more common in females by a 3:1 ratio.

Etiology
Exact etiology is uncertain. The most recent attempts to define the disorder have focused on genetics and molecular biology.

Localization
Any bone in the body can be affected. In the head and neck the skull and facial bones are affected in 10-20% of cases of monostotic disease and 50% of polyostotic cases. In cases with involvement of the temporal bone, the disease is predominantly monostotic. The tympanic, mastoid, squamous or petrous temporal bone may be involved. Other unusual sites include the internal auditory canal, the lateral semi-circular canal and the ossicles. In a retrospective analysis of patients with fibrous dysplasia affecting the skull base, Lustig et al found the temporal bone to be affected in 24%.

Clinical features
The main clinical features of disease affecting the temporal bone are: (i) progressive loss of hearing, mostly conductive but which can be sensorineural and profound in some cases, (ii) temporal bone enlargement with progressive bony occlusion of the external auditory meatus, (iii) facial nerve palsy in some patients when the process affects the seventh cranial nerve, (iv) constriction of the ear canal may result in development of an epidermoid cyst lateral to the tympanic membrane likened to cholesteatoma by Megerian et al [1698].

Macroscopy
The affected bone is often expanded and the marrow is replaced by firm grey/tan tissue depending on the proportion of bony, fibrous and cartilaginous elements. There may be cyst formation.

Histopathology
The lesion consists of irregular trabeculae of woven bone arising abruptly from a bland spindle cell stroma. The trabeculae may be curved and shaped like letters in the Chinese ideogram and are devoid of a rim of osteoblasts. There is no nuclear atypia and mitoses are few. The proportion of fibrous and bony tissue is variable. The lesion may include benign cartilage. Secondary changes include osteoclast giant cells, foamy histiocytes and aneurysmal bone cyst formation.

Genetics
Polyostotic fibrous dysplasia (POFD) may occur in the setting of McCune-Albright syndrome, caused by activating mutations in the complex GNAS locus on chromosome 20 [327,527,577].

Prognosis and predictive factors
Fibrous dysplasia has rarely been associated with malignant transformation including osteogenic sarcoma, fibrosarcoma and chondrosarcoma, but the temporal bone is not one of the sites where this change has been described.
Osteoma and exostosis

Definition
Benign bony enlargement of the deeper portion of the external auditory meatus. There are two distinct forms. Exostosis is more common than osteoma.

ICD-O code
Osteoma 9180/0

Synonyms
Osteochondroma, osteocartilaginous exostosis.

Etiology
Exostosis appears to be related to trauma such as repeated exposure to cold water; in swimmers there appears to be an association with development of exostoses of the tympanic bone [769]. Exostoses have also been observed in individuals who routinely use stethoscopes, e.g. cardiologists [550]. The etiology of osteoma is not clear.

Localization
Osteoma is a very rare lesion, which is a single, unilateral, spherical mass on a distinct pedicle arising in the region of the tympanosquamous or tympanomastoid suture line. It has only occasionally been described outside the external auditory canal and the middle ear, developing in the mastoids, temporal bone internal auditory canal, glenoid fossa eustachian tube, petrous apex and styloid process.

Exostoses are common, broad-based lesions, often bilateral and symmetrical which are usually situated deeper in the ear canal than osteomas. In the bony portion of the normal external auditory meatus there are no adnexal structures and subcutaneous tissue and perios- teum combine to form a thin layer. Therefore the distance between the epidermal surface and underlying bone is small, which may explain the propensity for exostoses of the tympanic bone to develop in those who swim frequently in cold water [2121].

Clinical features
Symptoms are usually those of ear canal obstruction. Osteoma and exostosis are often associated with infection of the external canal on the tympanic membrane side. Surgical removal may be required to enhance drainage as well as to relieve the conducting hearing loss.

Histopathology
The osteoma is a spherical, pedunculated lesion composed of cortical lamellar bone on the outside overlying trabecular bone with intervening marrow spaces. The trabecular bone may show appositional woven bone formation. Normal squamous epithelium of the ear canal is often seen on the surface. The exostosis does not usually show marrow spaces. Both these lesions are distinct from the recently described benign fibro-osseous lesion of the superficial external canal [2121].

Prognosis and predictive factors
These are benign lesions with no potential for malignant transformation.

Fig. 7.12 A Osteoma of deep external canal. From L. Michaels & H. Hellquist (1711). B Exostosis of deep external canal. Note thin epidermal layer on the exostosis above and on the canal skin below and their proximity to the bone. In deeper sections, the exostosis merges gradually with the deep canal bone without pedunculation.

Fig. 7.13 A Exostosis. Coronal CT scan showing broad-based exostosis of deep external canal. B Osteoma. Axial CT scan showing a pedunculated osteoma of one external canal originating from the bone of deep external canal (arrow).
Angiolymphoid hyperplasia with eosinophilia

Definition
A benign vascular tumour with well formed, but immature, blood vessels, the majority of which are lined by plump, epithelioid (histiocytoid) endothelial cells. Subcutaneous examples are usually associated with a muscular artery. Most cases have a prominent inflammatory component in which eosinophils are a conspicuous feature.

Synonyms
Epithelioid haemangioma (ICD-O 9125/0), nodular angioblastic hyperplasia with eosinophilia and lymphofolliculosis, subcutaneous angioblastic lymphoid hyperplasia with eosinophilia and inflammatory angiomatoid nodule.

Epidemiology
There is a wide age range with a peak in the third to fifth decades and women are affected more often than men (759, 1945).

Etiology
Whether angiolymphoid hyperplasia with eosinophilia is a reactive lesion rather than a neoplasm is still debated. Features cited as supporting a reactive process include a history of trauma (10% of cases), its relationship around a larger vessel showing evidence of damage and the prominent inflammatory component (759, 1945).

Localization
The lesion occurs most frequently on the head, particularly the forehead and scalp (often in the distribution of the superficial temporal artery) and in the skin of the ear and the peri-auricular area. Other common sites are the distal parts of the extremities, especially the digits. Other skin surfaces may be involved and occurrences in oral mucous membranes, pharynx and orbit have been reported (759, 1945). Deep-seated sites are rare, as are an origin in a large vessel.

Clinical features
Most patients present with a nodule which has been present for a year or less; sometimes the lesion may have been present for as long as 15 years. In the skin, including that of the ear, the lesions which are often painful or pruritic, appear as dome shaped erythematous or hyperpigmented papules or nodules which may be excoriated and bleed easily. The pre-excision diagnosis is usually that of an angioma or epidermal cyst. There may be several nodules and these can become chronic and coalesce into confluent plaques. There is very little tendency for spontaneous resolution but systemic spread has never been reported. In some patients there is a peripheral blood eosinophilia.

Macroscopy
The lesions are usually 0.5-2.0 cm in diameter; they rarely exceed 5.0 cm. Those lesions which contain blood, resemble a haemangioma but in most cases the appearances are rather non-specific. Sub-cutaneous nodules may resemble a lymph node because of circumscription and a peripheral inflammatory/lymphoid reaction.

Histopathology
Histologically, there are both vascular...
Angiolymphoid hyperplasia with eosinophilia

There is a prominent proliferation of small, capillary sized blood vessels. Often there is a vaguely lobular pattern due to clustering of the capillary sized vessels around a medium sized thicker walled vessel. The vessels are lined by plump, epithelioid (histiocytoid) endothelial cells. The vessels look immature and may lack well-defined lumina; sometimes they appear as solid groups of cells. The nuclei of the endothelial cells are large, there is a finely distributed chromatin pattern and often there are central nucleoli. The cytoplasm may appear vacuolated. An inflammatory cell infiltrate with numerous eosinophils, mast cells and lymphocytes is present, though the numbers of eosinophils may vary considerably from case to case. In the peripheral zones of deeper lesions, formation of lymphoid follicles is often present. In deep seated lesions, there is commonly an associated larger blood vessel, usually a muscular artery; and the lining endothelial cells may also appear epithelioid. Dermal lesions are less well circumscribed and demarcated from the surrounding tissue then deeper lesions.

**Immunoprofile**
The epithelioid endothelial cells express CD31 and Factor VIII. CD34 is also expressed but usually only weakly. Immunostaining for actin can be helpful in demonstrating an intact myopericytic layer around the immature vessels. Mast cells are demonstrated by immunostaining with mast cell tryptase, CD117 (C-kit) or IgE (since mast cells bear receptors for IgE).

**Prognosis and predictive factors**
While there is no metastatic potential for this tumour, local recurrences following excision occur in up to one third of patients [1945]. The reasons for this are not clear. The recurrences might be the result of incomplete excision, re-growth from a persisting underlying vascular anomaly or merely a reflection of its neoplastic potential. Whatever the reason, follow-up after complete local excision is indicated.

Angiolymphoid hyperplasia must be distinguished from Kimura disease [450, 1322] with which it has been confused in

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<table>
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<tr>
<th>Clinical</th>
<th>Angiolymphoid hyperplasia with eosinophilia</th>
<th>Kimura disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Age most often</td>
<td>Women, 3rd and 5th decades</td>
<td>Men, young to middle age</td>
</tr>
<tr>
<td>Geographical</td>
<td>Worldwide</td>
<td>Most common in Far East, occasionally in Europe</td>
</tr>
<tr>
<td>Skin/subcutis</td>
<td>Red brown papules</td>
<td>Large disfiguring masses.</td>
</tr>
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<td>Forehead, scalp, ears</td>
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</tr>
<tr>
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<td>Often involved</td>
</tr>
<tr>
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<td>Sometimes</td>
<td>Almost always</td>
</tr>
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<td>Raised IgE</td>
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<td>Prognosis</td>
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<td>Excellent. Relapses common</td>
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</tr>
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</tr>
<tr>
<td>Lymphoid follicles</td>
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<td>Germinal centres</td>
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</tbody>
</table>

HEVs: high endothelial venules FDCs: follicular dendritic cells

Table 7.2 Clinical and histological features of angiolymphoid hyperplasia with eosinophilia (ALH E) and Kimura disease.
Kimura disease

Kimura disease is a chronic inflammatory condition of unknown etiology which presents as large, deep and often disfiguring, subcutaneous masses in the pre-auricular, parotid and submandibular regions. Often, there is enlargement of regional lymph nodes. Occasionally, only lymph nodes are involved. There is a peripheral blood eosinophilia and raised levels of IgE and the histological features are distinctive. Kimura disease is endemic in the Far East where it affects predominantly young to middle aged men with an age range of 11-80 years. However, the disease also occurs sporadically in Caucasians in the Western World. Histologically, the subcutaneous masses are found to be composed of lymphoid follicles surrounded by oedematous connective tissue rich in eosinophils and containing numerous thin walled blood vessels resembling high endothelial venules (HEVs). Infiltration of the germinal centres with eosinophils and follicle lysis is a frequent finding as is the presence of polykaryocytes. The polykaryocytes (cells with multilobed nuclei resulting from endoreduplication) in Kimura disease are derived from follicular dendritic cells. There is deposition of IgE on the processes of the follicular dendritic cells and there are also numerous mast cells, the latter well shown by immunostaining with antibody to IgE since mast cells bear receptor for IgE. Plasma cells may also be prominent. The disease is self-limiting with an excellent prognosis, though the lesions may recur.

The etiology is unknown. The raised levels of IgE, the IgE deposition in germinal centres and eosinophilia suggest the disease may be atopic in nature; and that the allergic response is results from lymphocyte-mediated interleukin-5.
**Idiopathic pseudocystic chondromalacia**

**Definition**
A non-neoplastic swelling of the pinna resulting from localized accumulation of fluid within elastic cartilage.

**Synonym**
Endochondral pseudocyst

**Epidemiology**
The lesion occurs mainly in young and middle-aged adults, although it has been reported in children. Minor degrees of this lesion may be present in any damaged ear cartilage.

**Etiology**
Minor trauma from repeated rubbing of the auricle may play a part. The fluid may exude from undamaged perichondrial vessels that cannot be absorbed by the damaged perichondrial vessels. Small pseudocysts of the elastic cartilage of the pinna may also be seen in the vicinity of inflammatory or neoplastic lesions of that region.

**Localization**
This condition occurs in any part of the ear cartilage.

**Clinical features**
The patient complains of painless swelling of a part of the ear cartilage.

**Macroscopy**
The gross appearance is one of a localized swelling of the auricular cartilage. The cut surface shows a well-defined cavity in the cartilage which is distended with yellowish watery fluid.

**Histopathology**
Microscopically the cavity shows a lining of degenerated cartilage on one surface; on the other surface the cartilage is normal.

**Immunoprofile**
There is no expression in the cells lining the cyst-like spaces for CD 31 or cytokeratins indicating that this is an accumulation of fluid in the elastic cartilage rather than an epithelial cyst or a vascular pseudocyst.

**Chondrodermatitis nodularis chronica helicis**

**Definition**
A non-neoplastic ulcerating nodule on the helix of the ear, which always involves the underlying cartilage.

**Synonym**
Winkler disease

**Epidemiology**
The condition occurs in the third or fourth decades in both sexes.

**Etiology**
Scleroderma-like changes in the vessels lead to the obstruction of small arteries of the perichondrium which comprise the primary lesions leading to cartilage necrosis. The acute inflammation and epidermal ulceration are secondary to the nearby cartilage necrosis.

**Localization**
The lesion occurs in the helix of the auricle, less commonly in the antihelix.

**Clinical features**
A small exquisitely painful ulcerating nodule forms on the auricle, usually in the superior portion of the helix.

**Macroscopy**
The nodule on the helix is ulcerated in its centre and shows cornified edges. Extruded necrotic cartilage may be seen in the floor of the ulcer.

**Histopathology**
There is ulceration of the skin of the auricle and complete necrosis of the superficial region of the elastic cartilage of the auricle. A piece of necrotic cartilage infiltrated by neutrophils and bacterial colonies may be present in the floor of the ulcer. The perichondrium of the elastic cartilage shows obstructive thickening of small arteries. Epidermis at the edge of the ulcerated lesion is hyperplastic.

**Prognosis and predictive factors**
The lesion is usually cured by surgical removal of the painful nodule.
Cholesterol granuloma and cholesteatoma

**Cholesterol granuloma**

**Definition**
Cholesterol granuloma is a foreign body giant cell reaction to crystals of cholesterol deposited in the middle ear cleft. It is accompanied by chronic otitis media.

**Etiology**
Cholesterol granuloma arises from haemorrhage derived from the inflammatory tissue of cholesterol granuloma, the red cell membranes becoming degenerated to cholesterol.

**Localization**
The main site of cholesterol granuloma is the middle ear cleft. This includes the tympanic cavity and mastoid air cells. Pneumatized air cells at the apex of the temporal bone may also be the seat of an expanding destructive lesion of this type.

**Clinical features**
The tympanomastoid lesions do not, in themselves, produce symptoms. Symptoms of chronic otitis media may be present, however. Cholesterol granulomas of the petrous apex may grow and even invade the cochlea and into the cerebellopontine angle, producing a tumour like mass with hearing loss and life-threatening symptoms.

**Macroscopy**
Yellow nodules are seen in tympanic cavity and mastoid in this condition. The petrous apex lesions appear cystic, the contents being altered blood.

**Histopathology**
The yellow tympanomastoid lesions are composed microscopically of cholesterol crystals (dissolved away to leave empty clefts in paraffin-embedded histological sections) surrounded by foreign body type giant cells and other chronic inflammatory cells. Such cholesterol granulomas are almost always found in the midst of haemorrhage in the middle ear mucosa. Hemosiderin is often present within macrophages among the cells surrounding the cholesterol granuloma. The contents of petrous apex cystic lesions are altered blood, and cholesterol clefts with a foreign body giant cell reaction. The wall of such lesions shows granulation tissue with hemosiderin. Remains of low cuboidal (middle ear) epithelium and bone, representing the wall of a pneumatized air cell, may be seen in biopsies of this condition [49,1062].

**Cholesteatoma of the middle ear and petrous apex**

Cholesteatoma is a misnomer being neither cholesterol containing nor a neoplasm. Cholesteatoma is a cystic or “open” mass of keratin squames with a living “matrix”. Although it is not a neoplastic lesion, especially in the middle ear cleft, it may act like one in that it has a propensity to destroy tissue and to recur after excision.

**Acquired cholesteatoma of the middle ear**

**Definition**
A cholesteatoma associated with a perforated tympanic membrane is acquired.

**Epidemiology**
This entity is seen mainly in older children and young adults.

**Etiology**
It seems likely that the acquired cholesteatoma is derived from entry of external ear canal epidermis into the middle ear. Most cases are associated with severe otitis media in which entry of stratified squamous epithelium from the external ear epidermis through the tympanic membrane occurs. In some cases, it follows blast injury with perforation of the tympanic membrane at the time of the injury [1377]. Acquired cholesteatoma is also known to follow retraction

Fig. 7.19 Ear cholesterol granuloma. **A** An intact respiratory-type epithelium overlies the cholesterol clefts and foreign-body type giant cells seen in a cholesterol granuloma. **B** Innumerable histiocytes are seen adjacent to bone with areas of cholesterol cleft formation and inflammatory response.
Localization
The main site of origin of this lesion is the upper posterior part of the middle ear.

Clinical features
The patient presents with a foul-smelling aural discharge and conductive hearing loss. On examination of the tympanic membrane there is, in most cases, a perforation of the superior or posterosuperior margin.

Macroscopy
The cholesteatoma is seen as a pearly grey structure in the middle ear cavity associated with severe chronic otitis media.

Histopathology
Acquired cholesteatoma is usually "open" rather than "closed" or cystic. The pearly material of the cholesteatoma consists of dead, fully differentiated anucleate keratin squames. This is the corneal layer of the squamous cell epithelium. As in any normal stratified epithelium there are one to three basal layers of cells above which is a prickle (malpighian or spinous) layer composed of five or six rows of cells with intercellular bridges. The deeper layers of the epithelium of the cholesteatoma matrix frequently show evidence of increased proliferation reflected by down-growths into the underlying sub-epidermal connective tissue.

Immunoprofile
The excessive activity has been confirmed by: (a) the strong expression of cytokeratin 16, a marker for hyperproliferative keratinocytes, by cholesteatoma, but its absence in middle ear and external ear epithelium, except in the annulus region of the external tympanic membrane epithelium [278], (b) the strong expression of MIB-1, an antigen related to Ki-67, which also indicates hyperproliferative activity [2494], (c) counts of silver-stained argentophil nucleolar organizer regions, a technique which likewise displays proliferative activity, shows significantly larger numbers of these structures in the nuclei of acquired cholesteatoma as compared with those of the epidermis of the deep external auditory meatal skin [2496], (d) acquired cholesteatomatous epithelium shows an abnormally high concentration of IL-1, TGF-alpha, EGF-R and 4F2, all being growth factors [2495] indicating greater growth and differentiating activity than is present in normal epidermis.

Genetics
Acquired cholesteatoma does not show DNA aneuploidy nor does it possess an inherent genetic instability, a critical feature of all malignant lesions [33].

Congenital cholesteatoma of the middle ear

Definition
Congenital cholesteatoma is defined in clinical practice as a cholesteatoma of the middle ear which exists in the presence of an intact tympanic membrane, the implication being that severe chronic otitis media, which normally produces a perforation of the tympanic membrane, has not led to its development.

Epidemiology
This lesion is found in infants and young children.

Etiology
Small colonies of cells confirmed by immunohistochemistry as being epidermoid in nature are found near the tympanic membrane on the lateral anterior superior surface of the middle ear in every temporal bone after 15 weeks gestation. These “epidermoid formations”, are derived from the actively growing epidermis of the eardrum. They increase significantly in size with increasing age and at the same time show increasing epidermoid differentiation [1502]. In normal development, the epidermoid colonies disappear by the first post partum year. However, if one of them does not resolve, but continues to grow, this will become a congenital cholesteatoma.

Localization
The majority of cases are found in the antero-superior part of the middle ear.

Clinical features
In early lesions there are no symptoms,
the cholesteatoma being discovered by routine otoscopy. In later cases, the lesion is much larger and symptoms may resemble those of acquired cholesteatoma.

**Macroscopy**
In most cases a spherical whitish cyst in the anterosuperior part of the tympanic cavity is seen, behind an intact tympanic membrane. In 10% of congenital cholesteatomas the lesion is “open”, the desquamated squames entering the tympanic cavity.

**Histopathology**
The matrix of congenital cholesteatoma is epidermis, comprising a single row of basal cells, several rows of malpighian cells and a thin granular layer. The surface of dead, keratinous squames merges with the keratinous contents of the cyst, or keratinous lamellae in the case of the open type.

**Immunoprofile**
Immunostaining shows similar features to those of acquired cholesteatoma.

**Prognosis and predictive factors**
If removed early, when small, congenital cholesteatoma can be considered as cured. If left, or not diagnosed, until later in life, the problems of middle ear damage and recurrence become similar to those of acquired cholesteatoma.

**Cholesteatoma of the petrous apex**

**Definition**
An epidermoid cyst arising in the region of the petrous apex. It bears no relation to cholesteatoma of the middle ear.

**Etiology**
It is probably of congenital origin, but no cell rest has been discovered from which it might arise.

**Clinical features**
This lesion usually presents with facial palsy and hearing loss, due to involvement of the seventh and eighth cranial nerves, respectively, in the cerebellopontine angle [564].

**Histopathology**
The histological appearance is similar to that of middle ear cholesteatomas.
Adenoma of the middle ear

Definition
Adenoma is a benign glandular neoplasm showing variable differentiation along neuroendocrine and mucin-secreting pathways.

ICD-O code 8140/0

Synonyms
Middle ear adenomatous tumour, neuroendocrine adenoma of the middle ear, carcinoïd of the middle ear.

Epidemiology
This is an uncommon neoplasm, but among the most frequent ones arising in the middle ear. There is an approximately equal sex distribution, with an age range of 20-80 years, and a mean age of 45 years [2623].

Localization
The tumour arises anywhere in the middle ear cavity, sometimes extending into the mastoid. In one reported case it arose from the epitympanic part of the tympanic membrane [75]. In a small number of cases it may be found to have spread through the tympanic membrane [2623].

Clinical features
Patients complain of muffled hearing with a pressure sensation in the affected ear. Otoscopy shows an intact tympanic membrane in the first stage with a dark brown-reddish coloured structure behind it. Tumour may later expand and involve the ossicular chain causing conductive hearing loss and may penetrate the tympanic membrane. Treatment is surgical. The tumour is usually easily removed, but if ossicles are entrapped reconstructive surgery is needed.

Macroscopy
The neoplasm has been described as being white, yellow, grey or reddish brown at operation and, unlike paraganglioma, is usually not vascular. Although not encapsulated it seems to peel away from the walls of the surrounding middle ear with ease, although ossicles may sometimes be surrounded by the tumour and may even show destruction.

Histopathology
Adenoma is formed by closely apposed small glands with a “back to back” appearance. In some places a solid or trabecular arrangement is present. Sheet-like, disorganized areas are seen in which the glandular pattern appears to be lost. This may be artefactual and related to the effects of the trauma used in taking the biopsy specimen, on the delicate structure of the cells, but the appearance may erroneously lead one to suspect malignancy. The cells are regular, cuboidal or columnar and may enclose luminal secretion. A distinct and predominant “plasmacytoid” appearance of the epithelial cells of the neoplasm may be displayed [2164]. The small central nuclei rarely contain nucleoli and show no significant mitotic activity. No myoepithelial layer is seen. Periodic acid-Schiff and Alcian blue stains may be positive for mucoprotein secretion in the gland lumina and in the cytoplasm of the tumour cells. Soon after adenoma of the middle ear was described in 1976 [588,1160], it was reported that some glandular tumours of the middle ear, otherwise apparently identical to an adenoma, showed neuroendocrine features as shown by Grimelius positivity, the presence of numerous membrane-bound granules on electron microscopy, and expression of immunohistochemical markers for neuroendocrine activity. The concept of “carcinoid tumour” evolved, i.e. that this was a distinct neoplasm with significant neuroendocrine differentiation. As with carcinoids in other locations, it was considered to have malignant potential. It is now clear that most, probably all, middle ear adenomas express neuroendocrine markers [2623,2727].

Immunoprofile
Neuroendocrine markers such as synaptophysin, chromogranin, and various polypeptides, are demonstrated in addition to cytokeratins [2623].

Electron microscopy
Ultrastructural examination of five cases showed basally situated cells and solid tumour containing neuroendocrine granules which were positive for neuroendocrine markers. This is in contrast to apically situated dark cells which contained mucous granules and were negative for neuroendocrine markers [2727].

Precursor lesions
The lesions arise from the lining epithelium of the middle ear. Under appropriate stimuli such as otitis media, this epithelium has the potential for glandular differentiation. However, neuroendocrine differentiation has not been demonstrated in either normal or “metaplastic” glandular epithelium.

Genetics
There has so far been no study of molecular genetic aspects of this tumour. This neoplasm does not occur in families.

Prognosis and predictive factors
There have been a few recurrences after incomplete local surgical excision.
**Aggressive papillary tumour**

**Definitions**
Tumour with a papillary, non-stratified epithelial pattern showing invasive behaviour.

**ICD-O code** 8260/1

**Synonyms**
Primary adenocarcinoma of the middle ear of papillary type, aggressive papillary tumour of temporal bone, papillary adenoma.

**Epidemiology**
Forty-six cases with this neoplasm were collected from the literature in 1994 [843]. Some of these had been reported as low-grade adenocarcinoma of probable endolymphatic sac origin [1038]. Review of each of the case reports in these two studies, together with cases reported more recently, reveals a total of 24 cases in which the middle ear was involved, comprising 17 females and 7 males. The age-range at time of diagnosis was between 16 and 55 years with a median age of 33 and a mean age of 34 years. In many of the cases, however, the patient had already suffered symptoms subsequently ascribable to the tumour for some years when the diagnosis was made, so that the age of onset may be considerably younger than is suggested.

**Localization**
The tumour is found in any area of the middle ear, including the mastoid process and air cells and may fill the tympanic cavity. In all of the described cases, except two [519,2481] there was extensive invasion outside the middle ear, involving the apical portion of the petrous bone in most and in a few the tumour reached the cerebellopontine angle and the cerebellum.

It has been suggested that cases of aggressive papillary middle ear tumour with widespread involvement of the temporal bone may arise from a primary papillary adenocarcinoma of the endolymphatic sac [1038]. The frequent association of papillary tumours in the middle ear with apical petrous bone neoplasia of the same type, the similarity of the histological appearances of the neoplasms in the two regions and the association of some cases of papillary tumours in both regions with von Hippel-Lindau disease would seem to favour this concept, but an origin in the middle ear in some cases of this neoplasm has not been definitely excluded. This would explain the presence of the neoplasm in the middle ear only in two described cases. In the single description of the pathological changes of aggressive papillary tumour of the middle ear in an autopsied temporal bone, widespread deposits of tumour at inner ear sites are depicted, but no mention is made of involvement of the endolymphatic sac or duct [2355]. Whatever the site or sites of origin of this tumour it should be recognized that papillary epithelial tumour of the middle ear is frequently an aggressive neoplasm, in contrast to the non-papillary adenoma of the middle ear which is quite benign [1741].

**Clinical features**
In most cases of this neoplasm clinical and audiological features point to a middle ear lesion. Suspicion of a neoplasm of the middle ear is enhanced by the oto-scopy features in a few cases. Indeed, the tympanic membrane has been perforated by the tumour, which is seen to lie in the external canal in some cases. On imaging the medial parts of the petrous temporal bone show, in the great majority of cases, areas of involvement by a lytic lesion, representing an invasive neoplasm which may extend posteriorly outside the temporal bone and invade the cerebellum [843]. Fifteen percent of patients with aggressive papillary tumour of middle ear have been found to possess neoplasms or other manifestations of Von Hippel-Lindau syndrome. There may be a family history of this condition in the patient without its actual physical manifestations [843].

**Histopathology**
The middle ear cleft, including the mastoid air cells, is usually filled with the papillary tumour. Bone invasion is often seen. A papillary glandular pattern is present.
Papillary tumours of the middle ear

with complex interdigitating papillae lying loosely or infiltrating fibrous connective tissue. The papillae are lined by a single layer of low, cuboidal to columnar epithelial cells with uniform nuclei, eosinophilic cytoplasm and indistinct cell borders. Thyroid follicle-like areas may be present, similar to those seen in endolymphatic sac carcinoma.

**Immunoprofile**

Markers for cytokeratin, epithelial membrane antigen and S100 are positive. The absence of thyroglobulin must be determined to exclude metastatic papillary carcinoma of the thyroid. Markers for CK7, CK20 and carcinoembryonic antigen may also be useful to exclude metastatic deposits from lung and colon.

**Genetics**

The genetic aspects of von Hippel-Lindau disease are described below. In view of the association of some cases of that condition with aggressive papillary middle ear tumours it is suggested that the clinical assessment of each case with the latter neoplasm should include an investigation for the gene mutations of von Hippel-Lindau disease.

**Schneiderian-type papilloma**

Schneiderian epithelium refers to the normal respiratory-type ciliated epithelium of the nose and paranasal sinuses. Schneiderian papillomas are tumours of the nose and paranasal sinuses that are stated to be derived from this epithelium. Three such types of papillomas are described: inverted (endophytic), exophytic and endophytic growth. Intermediate types are said to be found between the three forms. Inverted or “endophytic” features comprised only a portion of the tumours in the two cases. In Case 2 the term transitional cell papilloma was used. This is a term that has frequently been applied to describe everted squamous cell papilloma. In this case inverted papilloma was found in the nasal cavity and it was suggested that the papillomas might have spread from there to the middle ear by way of the

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Eustachian tube. In Cases 1, 4 and 10 “inverted papilloma” were found in the middle ear concomitantly with in situ or invasive squamous carcinoma and it seems possible that the “inverted papilloma” areas might have been, in reality, areas of low grade squamous carcinoma.

We would suggest that a good case has not been made for the occurrence of inverted papilloma in the middle ear. Some of the lesions may have been papillomas of the middle ear as described above. In Case 2 inverted papilloma could conceivably have colonized the middle ear from the nasal cavity. Further detailed descriptions of the entity are required to justify the diagnosis of such a diagnostic category in this situation.

### Inverted papilloma

**Definition**

Papillary neoplasm of the middle ear which is histologically identical to that occurring in the sinonasal region.

**ICD-O code** 8121/1

**Localization**

Middle ear. Also occurs in association with similar papillomas of the upper respiratory tract, either by direct continuity or in a multicentric fashion.

**Clinical features**

It usually presents as chronic otitis media.

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**Definition**

A choristoma in contrast to a hamartoma, is composed of tissues which are not normally present in the part of the body where it is found. Choristomas are occasionally seen in the middle ear. They are composed of one or other of two types of tissue: salivary gland or glial tissue.

### Salivary gland choristoma

**Localization**

This lesion usually occurs as a mass in the middle ear attached posteriorly in the region of the oval window. There are usually absent or malformed ossicles [1093].

**Histopathology**

Salivary gland choristomas consist as a rule of lobulated mixed mucous and serous elements like the normal submandibular or sublingual gland, but unlike the parotid gland.

**Glial choristoma**

**Clinical features**

In this lesion, masses composed of glial tissue are identified in biopsy material from the middle ear. A bony deficit with consequent herniation of brain tissue into the middle ear should be ruled out by imaging [1257].

**Histopathology**

Glial masses are present, composed largely of astrocytic cells with large amounts of glial fibrils.

**Immunoprofile**

The identity of the tissue as glial may be confirmed by immunohistochemical staining for glial acidic fibrillary protein.

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**Macroscope**

Polypoid tumour filling the middle ear cavity.

**Prognosis and predictive factors**

Thus far, these tumours have shown no evidence of invasion but recurrences are common [2757].
Squamous cell carcinoma of the middle ear

Definition
A malignant tumour composed of stratified squamous epithelium arising from the cuboidal and / or pseudostratified epithelium of the middle ear.

ICD-O code
8070/3

Synonyms
Epidermoid carcinoma, squamous carcinoma

Epidemiology
The disease affects males and females equally, with an age range of 34-85 years and an average age of 60 years.

Etiology
An origin from long-term chronic inflammation of the middle ear has been suggested. However, malignant neoplasia in its earlier stages has clinical features similar to those of chronic otitis media. Moreover biopsy is not usually carried out during surgery when a diagnosis only of otitis media has been made. Therefore, longstanding squamous carcinoma of the middle ear may go undiagnosed.

Localization
The neoplasm soon expands to involve much of the middle ear. There is extension by tumour through the bone on the medial wall of the Eustachian tube to infiltrate the perineurium of nerves in the carotid canal. The tumour also penetrates the thin layer of bone between the posterior mastoid air cells and the dura with subsequent invasion along the dura and into the internal auditory meatus. Bilateral squamous cell carcinomas of the middle ear have been described [1713].

Clinical features
This tumour is usually advanced at presentation. The patient usually complains of pain in the ear, bleeding and a serosanguinous discharge from the ear canal. In those cases with a concomitant external canal carcinoma a plaque-like or even polypoid mass may be felt or even seen in the canal. Seventh nerve palsy is an important sign indicating infiltration beyond the middle ear.

Macroscopy
A tumour fills the middle ear and may extend into the mastoid air cells and along the pathways described above.

Histopathology
The neoplasm is a keratinizing squamous cell carcinoma with a variable degree of differentiation. Atypical change and even carcinoma in situ may be seen in some parts of the middle ear epithelium adjacent to the tumour. The tumour arises from malignant stratified squamous epithelium and in certain areas an origin directly from basal layers of cuboidal or columnar epithelium may be seen.

Precursor lesions
There is no evidence of a relationship to cholesteatoma or the epidermoid cell rests which normally occur in the middle ear during development.

Prognosis and predictive factors
The prognosis is uniformly poor and does not correlate with degree of tumour differentiation.

Fig. 7.26 Squamous carcinoma. Autopsy temporal bone specimen showing infiltration of squamous carcinoma of middle ear into mastoid air cell.
Meningioma of the middle ear

**Definition**
Meningioma is a benign tumour usually forming intracerebrally, but sometimes seen involving bony structures around the brain including the middle ear. It arises from the pia-arachnoid cells of the meninges.

**ICD-O code**
9530/0

**Epidemiology**
Meningioma of the middle ear affects women more than men, shows an age range of between 10 and 80 years with a mean age of 49.6 years. Female patients present at an older age (women 52.0 years, men 44.8 years) [2597].

**Localization**
Meningiomas occur at a number of sites in the temporal bone, including the internal auditory meatus, the jugular foramen, the geniculate ganglion region and the roof of the Eustachian tube [1830]. The most common temporal bone site for primary meningioma is in the middle ear cleft. In a recent study (36 patients), most tumours involved the middle ear, but a few involved adjacent structures such as the external canal or temporal bone. Only two showed extension from CNS on imaging [2597].

In neurofibromatosis type 2 (NF-2 see below), meningioma-like masses occur commonly in the internal auditory canal and cerebellopontine angle.

**Clinical features**
Patients present clinically with hearing change, otitis media, pain, and/or dizziness / vertigo.

**Macroscopy**
Gross appearances are those of a granular mass with a gritty consistency.

**Histopathology**
Microscopically the neoplasm in the middle ear shows the same histological features of any of the well-described subtypes of intracranial meningioma. The most common variety seen in the middle ear is the meningothelial type, in which the tumour cells form masses of epithelioid, regular cells often disposed into whorls. Occasionally, fibroblastic and psammomatous variants are seen.

**Immunoprofile**
Histological diagnosis may be difficult because the typical features of meningioma are absent. Under these circumstances immunocytochemistry is of diagnostic value. Vimentin and epithelial membrane antigen are expressed in the majority of meningiomas and cytokeratins are uniformly negative. Expression of S-100 protein identifies spindle cell tumours as of neurogenic origin, thus excluding spindle cell meningioma.

**Prognosis and predictive factors**
Although Nager’s review of temporal bone meningiomas (1964) indicated that only two out of 30 patients survived a 5-year period [1830], more recent experience of middle ear meningiomas signals a better outlook after careful local excision (5-y survival, 83%).

Fig. 7.27 Meningioma of middle ear. A Meningioma of middle ear, meningothelial type, showing small whorls. B Ear meningioma. A variety of different growth patterns can be seen, but the meningothelial nature of the neoplasm is always maintained.
Vestibular schwannoma

Definition
A benign nerve sheath tumour arising in the internal auditory canal.

ICD-O code 9560/0

Synonyms
Acoustic neuroma, acoustic neurinoma, neurilemmoma

Epidemiology
Vestibular schwannoma is the most common neoplasm of the temporal bone. Unilateral vestibular schwannoma accounts for 5-10% of all intracranial tumours and for most of the cerebellopontine angle tumours. It is found in about 0.8% of consecutive adult necropsies (1475). The age at presentation is the fifth or sixth decade. It also is seen in younger people in association with neurofibromatosis type 2.

Etiology
Solitary vestibular schwannoma occurs sporadically, and does not seem to be associated with a gene mutation. The etiology is unknown.

Localization
Vestibular schwannoma was formerly considered to arise most commonly at the glial-neurilemmal junction of the eighth cranial nerve. Such a site of origin has now become doubtful (2834). In one study of five temporal bones with small vestibular schwannomas, the tumour arose more peripherally (2834). The vestibular division of the nerve is usually affected. Rarely, the cochlear division is the source of the neoplasm. Growth takes place from the site of origin of the tumour, both centrally onto the cerebellopontine angle and peripherally along the canal. Vestibular schwannoma is usually unilateral, but may be bilateral, in which case the condition is neurofibromatosis 2.

Clinical features
Progressive unilateral hearing loss (90% of patients) and tinnitus (70% of patients) are the clinical manifestations, due to cochlear involvement. Less common symptoms are: headache, vertigo, facial pain and facial weakness. The neoplasm may grow slowly for years without causing symptoms and may be first diagnosed only at post-mortem. Diagnosis is usually made by MRI scanning. In small, slowly growing tumours, an option for management is non-surgical, using MRI scanning at intervals to observe growth. Surgical removal may be carried out by drilling from the external canal through the temporal bone or by craniotomy and middle fossa approach to the internal auditory meatus, or by stereotactically guided gamma knife surgery.

Macroscopy
The neoplasm is of variable size and shape. Small tumours either do not widen the canal at all or produce only a small indentation in the bone. The larger tumours often have a mushroom shape with two components, the stalk - a narrower, elongated part in the canal - and an expanded part in the region of the cerebellopontine angle. The bone of the internal auditory canal is widened funnel-wise as the neoplasm grows. The tumour surface is smooth and lobulated. The cut surface is yellowish, often with areas of haemorrhage and cysts. A multicyctic vestibular schwannoma has been described (1804). The vestibular division of the eighth nerve may be identified on the surface of the tumour and attached to it while the cochlear division is often stretched by the neoplasm, but not attached to it.

Histopathology
Vestibular schwannoma is a neoplasm of the nerve sheath / Schwann cells. This tumour typically shows closely packed spindle cells, often with palisaded nuclei and Verocay bodies (Antoni A areas) and less cellular areas with a loose reticular pattern and microcystic degeneration sometimes containing numerous xanthoma cells (Antoni B). The degree of cellularity of the neoplasm can be high or low. The spindle cells frequently are moderately pleomorphic, but mitotic figures are rare. The presence of pleomorphism does not necessarily denote a malignant tendency, but in rare cases undoubted malignant changes can appear associated with an increased growth rate (120). Thrombosis and necrosis may be present focally. Tumour extension into the modiolius or vestibule along cochlear or vestibular nerve branches may be present even in solitary vestibular schwannomas, although more common in NF-2. Granular or homogeneous fluid exudate is usually present in the perilymphatic spaces of the cochlea and vestibule. This may arise as a result of pressure by the neoplasm on veins draining the cochlea and vestibule in the internal auditory meatus. Hydrops of the endolymphatic system may occur and in larger tumours there is atrophy of spiral ganglion cells and nerve fibres in the basilar membrane.

Fig. 7.28 Vestibular schwannoma. A Microsliced autopsy temporal bone. The neoplasm arises from the vestibular division of the eighth nerve and compresses the cochlear division. Note the granular deposit lining the cochlea, a feature of most larger vestibular schwannomas. From L. Michaels & H. Hellquist (1711). B Axial T2 post-contrast MRI scan of the posterior fossa showing a well-defined intracanalicular vestibular schwannoma (arrow). Note the eighth cranial nerve leading into the tumour.
**Immunoprofile**

These tumours express diffuse, strong nuclear positivity for S-100 protein. Vimentin expression is also usually positive though not specific. These findings are common to both unilateral vestibular schwannoma and the schwannomas of NF2. Glial fibrillary acidic protein and neuron specific enolase markers may also be expressed. The tumours are consistently negative for CD34, a marker widely used for the diagnosis of solitary fibrous tumours, unless there are widespread degenerative changes [2625]. The proliferation marker Ki67 has demonstrated that tumours 18 mm or smaller in diameter have lower proliferation indices and growth rates than tumours larger than 18 mm [186]. The proliferation index in vestibular schwannoma associated with NF-2 is higher than in solitary vestibular schwannomas [17].

**Electron microscopy**

Schwann cells are identified as the cell of origin by their interdigitating slender cytoplasmic processes covered with a continuous layer of basal lamina [434]. Extensive degeneration of the vestibular sensory organ as detected ultrastructurally is brought about by growth of the neoplasm from the vestibular division of the eighth nerve. Even small tumours may cause this change [2241].

**Genetics**

Ninety five per cent of vestibular schwannomas are unilateral and are sporadic. Less than 5% of tumours are bilateral and therefore associated with the NF2 gene. The risk that a unilateral tumour is the first indication of NF2 is closely related to the age of the patient. Young patients under the age of 25 are at high risk of developing contralateral tumours and NF2 while patients with unilateral tumours who are over the age of 55 have virtually no risk of developing NF2. There is no increased incidence of unilateral vestibular schwannoma or NF2 in the offspring of patients with unilateral vestibular schwannoma [1595].

**Microneuromas and Paget disease of bone**

**Definition**

Small non-neoplastic tumours composed of masses of intertwined bundles of nerve fibres and Schwann cells, which are sometimes observed near the cochlea or vestibule in the temporal bones of cases of Paget disease of bone. It is likely that they are the result of pressure by the growth of the pagetic bone on the nerve fibres with their regeneration and the production of traumatic neuromas [2275].

**Prognosis and predictive factors**

Size is an important aspect in the prognosis of cases of vestibular schwannoma. Tumours 18 mm or smaller in diameter have lower proliferation indices and growth rates than tumours larger than 18 mm [186].
Neurofibromatosis type 2

Definition
An autosomal dominant disorder characterized by a high incidence of bilateral vestibular schwannomas as well as schwannomas of other cranial and peripheral nerves, and other benign intracranial and intraspinal tumours.

Synonym
Bilateral acoustic neuroma, bilateral vestibular schwannoma

Epidemiology
The condition usually presents clinically in the first or second decade of life.

Localization
Bilateral vestibular schwannoma is characteristic of neurofibromatosis type 2. The tumours usually arise from the superior vestibular branch of the 8th cranial nerve. In addition, schwannomas of other cranial and peripheral nerves do occur as well as a wide variety of other benign intracranial and intraspinal tumours including schwannoma of other cranial and peripheral nerves, meningiomas, ependymomas, spinal neurofibromas, and gliomas. Juvenile posterior subcapsular cataract is also found.

Clinical features
Vestibular schwannomas in NF2 patients grow more rapidly than sporadic unilateral tumours. Infiltration of the cochlear and facial nerves occurs, making it more difficult to preserve hearing and facial nerve function after surgery. Screening of the relatives of affected subjects is necessary. Affected relatives of these patients often have normal audiograms and normal auditory brain stem responses in the presence of a schwannoma, and it has been recommended that the screening of relatives of NF2 patients should be by magnetic resonance image scanning with gadolinium (Gd-DTPA) enhancement [1326].

In contrast to NF2, neurofibromatosis type 1 or von Recklinghausen disease is characterized by dermal neurofibromas. However, otological manifestations of neurofibromatosis were recorded in 6.5% of children with NF1, involving external ear canal, middle ear and eighth cranial nerve [2415].

Macroscopy
The gross appearance of the vestibular schwannomas in neurofibromatosis 2 is similar to that of sporadic vestibular schwannoma.

Tumour spread and staging
There is invasion of the facial nerve in the internal auditory canal and also invasion of the modiolus and bony vestibular wall in some cases [2354].

Histopathology
Vestibular schwannomas in NF2 are similar to those of sporadic vestibular schwannoma.

Immunoprofile
The degree of labelling with the proliferation marker Ki67 is higher in cases of NF2 that in those of solitary vestibular schwannoma [17]. Otherwise, the immunoprofile is identical.

Genetics
NF2 is an autosomal dominant condition. About 50% of patients have NF2 as a result of a new mutation and 50% inherit the disease from an affected parent. The children of an affected person have a 50% chance of inheriting the disease and prenatal diagnosis is available. The gene for NF2 is a suppressor gene which has been mapped to the long arm of chromosome 22 (22q12). It codes for a protein which has been called by two names; MERLIN which stands for moezin-ezrin radixin like protein because it resembles the family of cytoskeletal associated proteins and SCHWANNOMIN because of its role in preventing schwannoma formation. It is a membrane-associated protein believed to inhibit cell growth and motility and preserve cell shape as well as anchoring the cell cytoskeleton to the surrounding matrix. Studies aimed at identifying germline mutations in patients with NF2 found mutations in up to 2/3 of cases. A wide variety of mutations have been found in all exons of the NF2 gene apart from exons 16 and 17. Ninety per cent of the mutations are predicted to truncate the gene product by introducing a stop codon, a frameshift with premature termination or a splicing alteration. This suggests that loss of the protein’s function is necessary for tumourigenesis [1595].

A family on the Isle of Man, Great Britain, with inherited salivary gland neuroendocrine carcinoma and amelogenesis imperfecta [1712] also displayed vestibular schwannoma in two male sibs, bilateral in one. Molecular genetic analysis has not yet been carried out, but it is likely that the disease process in this family is genetically related to NF2.
Lipoma of the internal auditory canal

Definition
A benign tumour of adipocytes, important in this situation because it can mimic vestibular schwannoma.

ICD-O code 8850/0

Localization
Either in the cerebellopontine angle or in the internal auditory canal.

Clinical features
The most frequent associated symptoms are of cochleovestibular origin, such as hearing loss, dizziness and unilateral tinnitus. Other associated symptoms involve the facial nerve or the trigeminal nerve. Complete resection is associated with cranial nerve damage [2557]. The lesion may be mistaken clinically for a schwannoma, but magnetic resonance imaging can distinguish between the two entities. Where there is doubt, frozen section diagnosis of an incisional biopsy should be carried out to avoid the risk of damage to the 7th or 8th cranial nerve or their branches which may pass through the tumour.

Macroscopy
There may be erosion of the walls of the internal auditory canal as with vestibular schwannoma, and lipoma may appear similar to the latter at operation.

Histopathology
The tumour is similar to lipomas elsewhere except that 7th or 8th cranial nerve or their branches may be present among the adipocytes [2375].

Haemangioma

Definition
A benign tumour of blood vessels.

ICD-O code 9120/0

Synonyms
Cavernous haemangioma, vascular tumour, vascular malformation.

Etiology
Little is known about these rare tumours. Only 43 cases were reported in the world literature up to the year 2000 [2313]. They are thought to arise from the dense vascular networks around the geniculate ganglion and Scarpa ganglion, which may account for the site predilection.

Localization
Haemangioma of the temporal bone occur most frequently at two sites, the internal auditory meatus and the geniculate ganglion [1669]. Cavernous haemangioma arising in the cerebellopontine angle can mimic vestibular schwannoma, which occur more commonly at this site.

Clinical features
Patients may present with hearing loss or facial paralysis due to VIIth cranial nerve involvement, which usually happens at an early stage, before the tumour reaches 1 cm diameter. Symptoms are suggestive of haemangioma if they are disproportionate to the size of the lesion as seen on imaging, or fluctuate with hormonal changes such as occur in pregnancy. MRI imaging shows a lesion that enhances with gadolinium and which may contain areas of microcalcification.

Histopathology
The lesions are composed of irregular dilated vascular spaces with collagenous walls lined by a single layer of endothelium.

Prognosis and predictive factors
Although they are benign lesions, haemangiomas enlarge and do not spontaneously involute. Early surgical intervention is recommended to best preserve facial nerve function.
Endolymphatic sac tumour

Definition
Endolymphatic sac tumour (ELST), a non-metastasizing adenocarcinoma of endolymphatic sac origin, is a slowly-growing tumour which widely invades the petrous bone.

ICD-O code 8140/3

Synonyms
Heffner tumour (1038), low grade adenocarcinoma of endolymphatic sac origin (LGAES), aggressive papillary middle ear tumour (APMET).

Epidemiology
A rare neoplasm of adults. Although ELST is extremely rare in the general population. An association with von Hippel-Lindau disease (VHL) is established (1696).

Etiology
The mutations in the VHL gene have been implicated in the development of ELST.

Localization
At an early stage of its growth, the neoplasm is sited within the endolymphatic sac (970,1026). At a later stage, it destroys much of the petrous bone, including the middle ear and extends to the posterior fossa into the cerebellopontine angle (1038,2767).

Clinical features
Tinnitus, hearing loss and vertigo, similar or identical to the symptoms of Ménéière disease, are present in about one third of patients. It is presumed that early obstruction of the endolymphatic sac leads to hydrops of the endolymphatic system of the labyrinth. As the tumour spreads, facial nerve paralysis and/or cerebellar disorders may develop. Imaging reveals a lytic temporal bone lesion, appearing to originate from the region between the internal auditory canal and sigmoid sinus (which is the approximate position of the endolymphatic sac). There is eventually prominent extension into the posterior cranial cavity and invasion of the middle ear.

Histopathology
In most cases, ELST has a variable papillary-glandular appearance, the papillary proliferation being covered by a single row of low cuboidal cells. The vascular nature of the papillae in some cases has given the tumour a histological resemblance to choroid plexus papilloma. Some cases show areas of dilated glands containing secretion which resembles colloid. Such thyroid-like areas may even dominate the histological pattern. A few cases show a clear cell predominance resembling carcinoma of the prostate and renal cell carcinoma. Despite controversy surrounding the origin of so-called “aggressive papillary middle ear tumour” (APMET see above) (844), current evidence suggests that it is ELST with extension into the middle ear.

Immunoprofile
These tumours express cytokeratin and some express glial fibrillary acidic protein. Specific markers for metastases including thyroglobulin and prostate-specific antigen are negative.

Genetics
The gene responsible for Von Hippel Lindau (VHL) has been mapped to the short arm of chromosome 3 (3p 25-26). Mutations in this gene have been reported in patients with ELST. The gene is thought to be a tumour suppressor gene since genetic analysis of tumours in patients with VHL disease supported Knudson’s hypothesis that an inherited mutation in one allele, followed by somatic mutation and loss of function of the second allele were required for tumorigenesis. In the case of sporadic tumours, tumourigenesis results from somatic mutation in both alleles of the tumour suppressor gene. A germline mutation of the VHL gene and somatic mutation of the wild type allele have been shown in ELST from VHL patients and somatic mutations in the VHL gene have been demonstrated in sporadic ELST. The rarity of ELST has meant that analysis of the tumours for specific mutations has been difficult. Hamazaki et al reported the genetic analysis of a case of ELST which

Fig. 7.34 Endolymphatic sac tumour. Axial T2 weighted MRI scan of the posterior fossa. The white area represents fluid within the endolymphatic sac and the grey area the solid component of the endolymphatic sac tumour.

Fig. 7.35 Endolymphatic sac tumour. A Mild atypical nuclei are identified at the luminal surface of the papillary projections. Thin fibrovascular cores are present. B Endolymphatic sac tumour showing thyroid-like glandular pattern.
occurred in the absence of VHL disease (984). This showed a nucleic acid substitution of G to T in nucleotide 546 in the VHL gene which resulted in an amino acid substitution (Trp to Cys codon117). An identical mutation has been reported in other VHL families. This suggests that the VHL gene is associated with ELST tumourigenesis with or without VHL disease.

**Fig. 7.36** A Normal endolymphatic sac showing papillary pattern of lining. B Endolymphatic sac tumour showing papillary pattern.

**Fig. 7.37** Endolymphatic sac tumour. A A dilated space contains a number of papillary projections, although it is lined by the same morphologically bland-appearing nuclei. B Simple papillary projections with areas of sclerosis. The cuboidal cells have an increased nuclear to cytoplasmic ratio.

**Prognosis and predictive factors**
The tumour grows slowly over many years and is not known to metastasize. Many tumours have already attained a large size at presentation. It is important to screen all patients with VHL for ELST by imaging so that small tumours may be detected early and completely excised (1696). Likewise, all patients with ELST should be screened for the VHL gene.

**Fig. 7.38** Endolymphatic sac tumour. Schematic representation of the VHL gene and site of mutations in ELST. The arrow indicates the site of mutation in exon 2. The 3' untranslated region (3'-UTR) is unshaded. Nucleotides are numbered according to the VHL cDNA sequence. From Hamazki et al. (984).
Haematolymphoid tumours

These tumours, in the WHO classification of haematological malignancies (1197), are primarily stratified according to lineage into myeloid, lymphoid, histiocytic/dendritic cell and mast cell neoplasms. In each category, neoplasms are defined according to morphology, immunophenotype, genetic features and clinical syndromes. For each type of neoplasm a cell of origin is proposed.

Ear lymphomas
Lymphomas occurring in and around the ear are rare compared to other sites. They may involve the pre- and retro-auricular lymph nodes, temporal bone or skin and soft tissue. Those lymphomas affecting the pre-auricular lymph nodes are predominantly disseminated or nodal.

Lymphomas of bone tend to occur with persistence of red marrow. With the exception of plasma cell tumours such as plasma cell myeloma (synonyms: multiple myeloma, myelomatosis) and plasmacytoma (synonym: solitary plasmacytoma of bone), both of which can involve the squamous and petrous temporal bone, lymphomas are extremely rare in the temporal bone. The mastoid process, part of the temporal bone, contains air cells and lacks marrow.

B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma (B-CLL / SLL)

ICD-O code 9823/3

Of those lymphomas resulting in cutaneous lesions of the head and neck, including the ears, the most common is B-cell chronic lymphocytic leukaemia/small lymphocytic lymphoma. Leukaemic infiltrates in the skin or leukaemia cutis are not rare. Lesions on the face including ears have been recognized for several decades as heralding the onset of B-CLL / SLL [352,353,2071,2265]. They are included in the section on ‘Cutaneous involvement in primary extra-cutaneous B-cell lymphomas’ in the WHO classification of skin tumours.

Classification of Skin Tumours
The B-CLL infiltrates may appear as macules, plaques, papules, nodules, ulcers and even bullous lesions. Such infiltrates occur at sites of previous herpes simplex or herpes zoster have been well documented [354]. Leukaemic infiltrates have also been observed at sites typical of lymphadenosis benigna cutis (earlobe, nipple, scrotum), a Borrelia burgdorferi-associated cutaneous B-cell pseudolymphoma [352], now called Borrelia-associated lymphocytoma cutis. Most cases of B-CLL with cutaneous infiltrates are not associated with decreased survival; those associated with a poor prognosis have exhibited progression of the underlying disease to a high-grade large B-cell lymphoma (Richter syndrome) [353,2884].

Histiocytic and dendritic cell neoplasms
Histiocytic and dendritic cell neoplasms are derived from the phagocytic and accessory cells, which have a major role in the processing and presentation of antigen to lymphocytes and which are bone marrow derived. The origin of the B-antigen presenting follicular dendritic cells remains to be established. They are not of bone marrow origin; an origin from either a fixed stromal/mesenchymal cell or from blood vessel endothelium are the two favoured options (1068).

Histiocytic and dendritic cell neoplasms are rare. Of these tumours, only Langerhans cell histiocytosis has a significant incidence of ear disease by virtue of involvement of the temporal bone and middle ear.

Fig. 7.39 B-CLL / SLL. Leukaemia cutis. A middle aged man presenting with infiltrates in the skin of the right and left ears including the ear lobes. The skin of his nose tip was also involved.

Fig. 7.40 A B-CLL / SLL, biopsy of ear lobe. High power view of a proliferation centre. Admixed with small lymphocytes, are the proliferating larger prolymphocytes with small nuclei and para-immunoblasts with prominent nucleoli. B Nuclear expression of Ki 67 showing a higher proliferation index in a proliferation centre than in the surrounding small lymphocytic component.
Langerhans cell histiocytosis

**Definition**
Langerhans cell histiocytosis (LCH) is a neoplastic proliferation of Langerhans cells, with expression of CD1a, S100 and the presence of Birbeck granules by ultrastructural examination.

**ICD-O code**
9751/1

**Synonyms**
Histiocytosis X, Langerhans cell granulomatosis. Clinical variants have been referred to as Letterer-Siwe disease, Hand-Schuller-Christian disease and solitary eosinophilic granuloma of bone.

**Epidemiology**
LCH is rare [1511]. The incidence is about 5 per million with most cases occurring in children [1887]. Bone involvement in LCH counts for less than 1% of all bone lesions. There is a wide distribution of age from a few months to the 9th decade of life [1066]. Males are affected more often than females and the disease is more common in Whites of northern European origin than Blacks.

**Etiology**
This is unknown. There may be an association with a history of neonatal infection but there is no evidence of viral involvement [1672].

**Localization**
Three overlapping syndromes are recognised [1511]. Unifocal disease occurs in the majority of patients and usually involves bone (solitary eosinophilic granuloma). It is the bones of skull which are particularly affected, followed in frequency by the femur, pelvic bones and ribs. Less commonly, unifocal disease is confined to a lymph node, skin or lung. LCH involving lungs in adults is nearly always associated with smoking and is thought to represent a different, possibly reactive disease [2684A]. In multifocal, unisystem disease (Hand-Schuller-Christian disease), several sites in one organ, almost always bone, are affected.

In multifocal, multisystem disease (Letterer-Siwe disease) many organs are involved such as bones, skin, liver, spleen, lymph nodes and bone marrow. Any bone may be involved, with the highest frequency occurring in the bones of the skull in children [1511]. In temporal bone disease the lesion involves the medial part of the external auditory meatus [2099].

**Clinical features**
Pain and swelling of the affected area is the most common presentation. In children with temporal bone involvement, the presenting features can simulate those of otitis media and mastoiditis because of otorrhoea and mastoid and facial swelling. Radiologically, early lytic lesions can suggest an aggressive disease process. Mutifocal unisystem disease is usually confined to young children, and the multiple destructive bone lesions are often associated with adjacent soft tissue masses. With skull bone involvement there may also be exophthalmos and diabetes insipidus if the pituitary is affected and tooth loss, if the jaw bones are involved. Multifocal multisystem disease usually occurs in infants and in addition to bone lesions, there are fever, skin involvement, hepatosplenomegaly and pancytopenia because of bone marrow involvement.

**Macroscopy**
The involved tissue is soft and usually red. If haemorrhage and necrosis are present, the colour may be yellow due to the presence of lipid and many eosinophils.

**Histopathology**
Crucial to the diagnosis is the recognition of the Langerhans cell. It is the nuclear appearances which are so distinctive; the nuclei are folded or grooved resembling a coffee bean or lobulated and indented. The nuclear chromatin is finely dispersed, nucleoli are inconspicuous and the nuclear membranes are thin. Mitotic activity is quite variable; sometimes there are up to 6 mitoses per sq. mm. In bone lesions Langerhans cells are found in nests and clusters. Necrosis is often present and should not be interpreted as suggesting aggressive disease. Admixed with the Langerhans cells are eosinophils, sometimes in large numbers, lymphocytes, neutrophils and plasma cells. Multinucleated osteoclast-like giant cells and lipid laden foamy macrophages can usually be identified. In old lesions foamy macrophages are numerous and there is significant fibrosis. The appearances of the lesions are so characteristic that the diagnosis can be made on cytological preparations, including touch preparations.

**Immunoprofile**
Neoplastic Langerhans cells resemble normal Langerhans cells in their expression of CD1a [675] and S-100 protein, the latter being expressed in both nuclei and cytoplasm [1835]. They also express CD4, vimentin, HLA DR and placental alkaline phosphatase (PLAP). CD68 and lysozyme are variably and only weakly expressed; and there is no expression of the follicular dendritic cell markers CD21 or CD35. Immunostaining for Ki67 shows a proliferation index of between 2% and 25%.

While their phenotype resembles that of normal Langerhans cells it is not identical, for in contrast their normal counterparts do not express placental alkaline phosphatase (PLAP) and also show differences in the expression of adhesion molecules [557].

**Electron microscopy**
As in normal Langerhans cells, neoplastic Langerhans cells contain the unique cytoplasmic organelle called the Birbeck or Langerhans granule. ‘Granule’ is something of a misnomer, since the characteristic shape is that of a tennis racket or long necked flask. These structures, which vary in length from 200-400 nanometres, are pentalaminar rods measuring 33 nanometres in width with a vesicular expansion at one end. They...
Langerhans cell histiocytosis arise from the cell membrane (1066). Their function is unknown.

**Genetics**
In all of the clinical syndromes/variants of LCH, studies of the X-linked androgen receptor gene have demonstrated that the proliferation of Langerhans cells is clonal (2796,2873).

**Prognosis and predictive factors**
It is the demonstration that Langerhans cell histiocytosis represents a clonal proliferation that has led to its acceptance as a neoplastic disorder. However, the prognosis for patients with either monostotic or limited polyostotic disease is good. Death is rare in LCH and is associated with disseminated forms of the disease. Thus the clinical outcome directly relates to the number of organs affected (946). The overall survival of patients with unifocal disease is 95% dropping to 75% with 2 organs involved and with further drops with increasing organ involvement. In about 10% of patients there is progression of unifocal lesions to multifocal disease. The presence of cytological atypia or an increased mitotic rate does not appear to correlate with prognosis (2181).

Fig. 7.41  A Langerhans cell histiocytosis, presenting as chronic otitis media due to involvement of the mastoid bone. High power view showing the distinctive Langerhans cells with their grooved and folded nuclei and some eosinophils.  B Langerhans cell histiocytosis, immunohistochemistry. Strong membrane expression of CD1a by neoplastic Langerhans cells. Note that in contrast to their normal counterparts they lack the long cytoplasmic extensions.  C Langerhans cell histiocytosis, immunohistochemistry. Strong expression for S100 in nuclei as well as cytoplasm.  D Langerhans cell histiocytosis, ultrastructure. High magnification showing the pentalaminar rod shaped structure of Birbeck granules.
Secondary tumours

Definition
Neoplasms which originate from sites other than within the structures of the ear i.e. external auditory canal, middle ear and temporal bone. These may be metastatic via blood or lymphatic channels from non-contiguous sites, or spread directly from a contiguous site by invasion of surrounding tissues or extension along / through existing channels.

Epidemiology
Secondary neoplasms in the ear / temporal bone are rare, amounting to 5-6% of 2,528 benign and malignant ear neoplasms compiled from surgical pathology accessions from four institutions (549). Among the 1,781 ear neoplasms listed from the U.S. Armed Forces Institute of Pathology, only 31 (1.74%) had “metastasized” to the ear, most of these to the middle ear. However, post-mortem histologic studies of temporal bones reveal metastatic cancer in 47 (22%) of 212 cancer patients (895), virtually all of whom had had disseminated disease. The epidemiology of metastases involving the temporal bone appears to be rare, although a recent review reported renal origin in 9% of cases (1748). However among 12 patients with occult carcinoma found incidentally at autopsy only one had distant metastases: prostate carcinoma with widespread bone metastases including temporal bone. Among 18 patients, “adequately treated” and clinically free of cancer, none had residual cancer at autopsy, including temporal bone (895).

Metastasis through direct extension
Direct extension into the ear / temporal bone occurs from the upper aerodigestive tract via the Eustachian tube and middle ear, and from the posterior fossa of the skull via the internal auditory canal. Direct invasion through bone and soft tissues occurs through the skull base and about the external ear in the parotid area. Head and neck primary tumours, excluding thyroid, account for the largest number (22%) of secondary tumours involving the ear by direct extension and/or invasion.

Localization
Blood borne metastases tend to localize to the petrous ridge (83%) and mastoid (28%) and are usually bilateral, multiple and associated with metastases to other bones. Contiguous spread via existing channels: anteriorly from the upper aerodigestive tract to the middle ear (21%) via the Eustachian tube (14.5%); posteriorly from the brain and meninges via the internal auditory meatus (28%) to the inner ear. Invasion of bone and soft tissue with extension into the base of the skull and external auditory canal and middle ear and mastoid occurs with paragan-

Table 7.4 Site(s) of origin of tumours metastatic to temporal bone (895,1863). Age range, 2 - 87 years.

<table>
<thead>
<tr>
<th>Site</th>
<th>Total number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>27 (22%)</td>
</tr>
<tr>
<td>Head and neck</td>
<td></td>
</tr>
<tr>
<td>incl. brain (7) and</td>
<td></td>
</tr>
<tr>
<td>choroid plexus (1)</td>
<td>26 (21%)</td>
</tr>
<tr>
<td>Lung/bronchi</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Malignant melanoma</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Unknown origin</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Miscellaneous other sites</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
</tr>
</tbody>
</table>

Clinical features
Metastases to the temporal bone generally occur late in the course of the disease. Signs and symptoms in 101 patients with a history of malignant neoplasm included hearing loss (28%), vertigo (10%) facial palsy (9%), tinnitus (7%), otalgia (5%), otorrhea (2%), external canal mass (2%), nystagmus (2), no symptoms (36%) (895,1863).

Histopathology
The secondary tumours maintain the phenotype of the primary. Since these secondary tumours occur in late stages of known malignant disease, evaluation of the unknown primary is rarely undertaken. Poorly differentiated malignancies invading the external auditory canal from a parotid lesion require consideration of parotid carcinoma, melanoma and adenocarcinoma of the canal. Biopsy of secondary temporal bone lesions, except for cerebellopontine angle tumours, is rarely undertaken and their origin is inferred by imaging studies, a history of malignancy or pathologic or cytologic studies of contiguous lesions.

Table 7.5 Temporal bone metastatic sites from 47 patients who died with malignancy University of Minnesota. From T.I. Gloria-Cruz et al. (895).

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petrous apex</td>
<td>83%</td>
</tr>
<tr>
<td>Mastoid</td>
<td>27.6%</td>
</tr>
<tr>
<td>Internal auditory canal</td>
<td>27.6%</td>
</tr>
<tr>
<td>Middle ear</td>
<td>21.1%</td>
</tr>
<tr>
<td>Facial nerve</td>
<td>19.7%</td>
</tr>
<tr>
<td>Eustachian tube</td>
<td>14.5%</td>
</tr>
<tr>
<td>Otic capsule</td>
<td>13.2%</td>
</tr>
<tr>
<td>Cochlea</td>
<td>10.5%</td>
</tr>
<tr>
<td>Vestibule</td>
<td>9.2%</td>
</tr>
<tr>
<td>External ear</td>
<td>9.2%</td>
</tr>
<tr>
<td>Membranous labyrinth</td>
<td></td>
</tr>
<tr>
<td>Cochlear duct</td>
<td>7.9%</td>
</tr>
<tr>
<td>Saccule</td>
<td>3.9%</td>
</tr>
<tr>
<td>Utricle</td>
<td>3.9%</td>
</tr>
<tr>
<td>Semicircular canals</td>
<td>3.0%</td>
</tr>
</tbody>
</table>