Rare Diseases of the Middle Ear and Lateral Skull Base

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ABSTRACT

Otalgia, otorrhea and hearing loss are the most common ear-related symptoms that lead to the consultation of an otolaryngologist. Furthermore, balance disorders and affections of the cranial nerve function may play a role in the consultation. In large academic centres, but also in primary care, the identification of rare diseases of the middle ear and the lateral skull base is essential, as these diseases often require interdisciplinary approaches to establish the correct diagnosis and to initiate safe and adequate treatments. This review provides an overview of rare bone, neoplastic, haematological, autoimmunological and infectious disorders as well as malformations that may manifest in the middle ear and the lateral skull base. Knowledge of rare disorders is an essential factor ensuring the quality of patient care, in particular surgical procedures. Notably, in untypical, complicated, and prolonged disease courses, rare differential diagnoses need to be considered.

Contents

1 Introduction

Otalgia, otorrhoea and hearing loss are among the most common ear-related symptoms leading to the consultation of an otorhinolaryngologist. Balance disorders and cranial nerve disorders may also play a role in the consultation. In addition to the most common diseases associated to these symptoms, such as acute otitis media, these symptoms can also point to systemic diseases that may initially present with an otological manifestation, but require further treatment by other medical specialties, e. g. internal medicine. Furthermore, hearing and balance disorders, tinnitus and disorders of the lower cranial nerves can indicate neurological diseases or be the first manifestation of tumours and lesions of the temporal bone. In addition to common diseases in which the ear, nose and throat (ENT) physician has clinical routine and safe treatment options are available, the differentiation of rare diseases of the middle ear and lateral skull base play a central role in both large academic centres and in primary care. Rare diseases of the middle ear and lateral skull base usually require an interdisciplinary approach in order to establish the correct diagnosis and initiate adequate treatment. A well-known symptomatology may conceal a rare entity, which, however, requires a different and more complex examination or further treatment compared to the more common diseases. As a consequence, a focus of this review is on rare osteological, neoplastic, haematological, autoimmunological and infectious diseases as well as on malformations that manifest in the middle ear and lateral skull base. An interdisciplinary cooperation is essential when the initial symptoms of a disease lead to the consultation of an ENT physician, but the diagnosis of a rare disease necessitates further treatment by other medical specialties. The middle ear and lateral skull base may be affected by all systemic diseases affecting bone and mucosa. ▶ **Table 1** shows an overview of the typical symptoms of diseases that may manifest in the middle ear and lateral skull base.

2 Malformations

2.1 Minor and major ear malformations

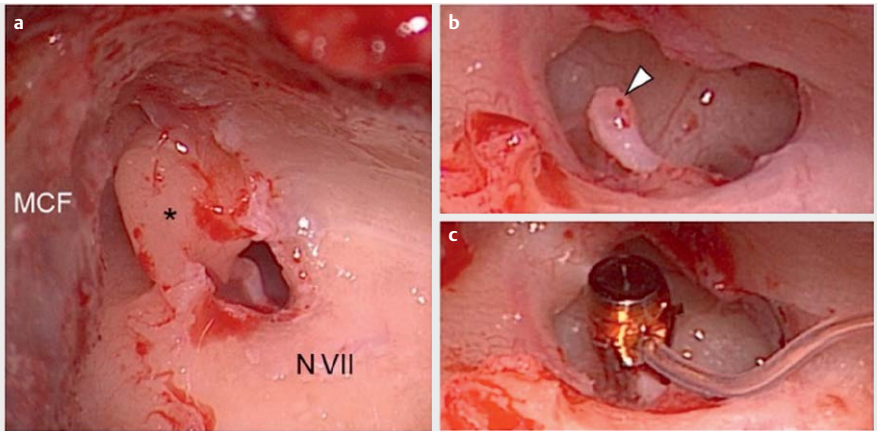
Malformations of the middle ear are often associated with malformations of the external ear (in particular the auricle) or may occur as part of syndromes. According to Jahrsdoerfer, they are subdivided into different degrees of severity depending on the extent and the structures involved [1–3]. The development of the middle ear and external ear occurs at different gestation times and can be disturbed by genetics or by drugs and medications. The combination with inner ear malformations is rare, but must be considered for later treatment [2, 4]. In the so-called “minor malformation”, there are normally wide middle ear spaces and external auditory canal. The ossicles, primarily the stapes are usually affected [5]. Other possible changes also affect other ossicles and can lead to fixation or interruption of the ossicular chain due to bony bridges, adhesions (▶ **Fig. 1**) or aplasia [6].

In a “major ear malformation”, the external auditory canal is not developed. This causes a backward displacement of the temporomandibular joint, resulting in an anterior displacement of the mastoid. The result is an underdevelopment of the middle ear space. Affected patients may at best have a rudimentary os tympanicum. Underdevelopment of the mastoid and external auditory canal can affect the course of the facial nerve in the Fallopian canal. There is a forward displacement of the nerve in the tympanic and mastoid course, which leads to a localization in the oval window or in the round window niche [7]. The incidence of major ear malformation lies between 1:8 000 and 1:10 000 [2, 8].

Malformations of the middle ear can also occur as part of syndromal diseases. 20–30 % of middle ear malformations occur bilaterally [9] and 7 % are associated with congenital malformations. A combi-

▶ **Table 1** Summary of selected rare differential diagnoses with manifestation in the middle ear and lateral skull base.

Disease	Symptoms	Specialities	Differential diagnosis	Diagnostics
Malformation				
Minor and Major Malformation	Visible malformation of the outer ear (major ear deformity) Conductive hearing loss (minor and major ear malformation)	Association to other (syndromal) malformations Increased surgical risk situation due to anatomical aberrations	Otosclerosis (minor ear malformation)	CT/ MRI: Malformation of anatomical structures (e.g. ossicles, vessels, nerves)
Diseases of the bone				
Morbus Paget	Conductive hearing loss	Conductive hearing loss of the inner ear Surgical thearpy not promising	Otosclerosis	Alkaline phosphatase elevated CT: Bone thickening
Osteogenesis imperfecta	Conductive hearing loss		Otosclerosis	Clinical manifestation CT: fractures Bone densitometry Genetic analysis
Fibrous Dysplasia	Mastoid swelling Stenosis of the external auditory canal	Clinical similarity to Hyperparathyreoidism	Exostoses of the external auditory canal	Calcium and phosphate normal, alkaline phosphatase elevated CT: Focal sclerotic milky glass-like bone expansion
Osteopetrosis	Tympanic effusions Stenosis of the external auditory canal Conductive hearing loss Facial nerve palsy	Fetal Stapes Bone thickening with narrowing of the neuroforamina	Otitis media Exostoses of the external auditory canal Idiopathic Facial nerve palsy	X-ray/CT: "Sandwich vertebrae", "bone-in-bone" phenomenon
Langerhans cell histiocytosis	Mastoid swelling Otorrhoea Dizziness Hearing loss	Fistulas of the external auditory canal	Otitis media Postoperative granulation tissue	CT: Osteolytic lesions, mastoid swelling. Biopsy: evidence of histiocyte infiltrates
Autoimmune diseases				
Granulomatosis with polyangiitis	Tympanic effusions Otalgia	Possible exacerbation after surgical intervention	Otitis media	Skin biopsy: non-specific leukocytoclastic vasculitis Nasal biopsy (high false negative rate) Granulomatous inflammation c-ANCA
Relapsing polychondritis	Inflammation of the cartilage of the auricle and/or the auditory canal	Involvement of the Eustachian tube	Otitis externa diffusa Perichondritis Erysipelas Otitis media Tympanic effusion	Clinical: Multilocular cartilage inflammation, polyarthritis, ocular involvement, cochleovestibular involvement.
Rheumatoid arthritis	Otorrhea Facial nerve palsy		Chronic Otitis media	Joint involvement Rheumatoid factors and/or antibodies against cyclic citrullinated peptide, CRP and/or ESR elevated
Neoplasms				
Benign Neoplasms	Painless swelling Hearing loss		Lymph node swelling Mastoiditis Exostoses of the external auditory canal	Biopsy
Malignant Neoplasms	(Bloody) Otorrhoea Hearing loss Otalgia Diplopia Balance disorders, dizziness Visual disturbances Hypaesthesia of the facial skin Facial nerve palsy	Chondrosarcoma: Destructions clivus and mastoid apex, early metastasis Metastases: Occurrence mainly in the petrous apex	Otitis media Mastoiditis	Biopsy
Paraganglioma	Hearing loss Pulsating tinnitus Otalgia Vertigo	Reddish pulsating mass behind the lower tympanic quadrants	Protruding bulb of the jugular vein Abnormal course of the internal carotid artery Schwannoma in the region of the jugular foramen Plasmocytoma Meningioma Neurofibroma	MRI: "salt-and-pepper" pattern Angiography: "Tumour Blush" PET-CT biochemical examination for catecholamine secretion
Neoplasms of the haematopoietic system				
Leukaemia Lymphoma Myeloma	Otalgia Otorrhoea Facial nerve palsy	Leukaemia: Occurrence mainly in the petrous bone apex	Otitis media	CT MRI Bone marrow puncture
Infectious diseases				
Tuberculosis Syphilis Necrotizing (malignant) external otitis Cholera	Otorrhoea Otalgia	Tuberculosis: Perforations of the tympanic membrane	Otitis media Otitis externa	Tuberculosis, cholera: microbiological pathogen detection by smear or biopsy Necrotizing (malignant) external otitis: CT (bony destruction)



▶ **Fig. 1** Auditory canal atresia in a case of major ear malformation in an 8-year-old child with conductive hearing loss. **a** Intraoperative view of the fixed malleus-incus complex (asterisk). **MCF:** middle cranial fossa; **NVII:** Facial nerve. **b** View on the stapes head (white arrowhead) after removal of the malleus-incus complex. **c** Coupling of the floating mass transducer of a Vibrant Soundbridge to the stapes head on the mobile stapes using a CliP Coupler.

nation with other malformations of the first two pharyngeal arches, such as mandibular hypoplasia, e. g. in oculo-auriculo-vertebral dysplasia (Goldenhar syndrome) is frequent [10]. Symmetrically occurring dysostosis mandibulofacialis (Treacher-Collins syndrome) shows hypoplasia of the mandible and zygomatic bone, a laterally sloping eyelid axis and eyelid anomaly [11, 12]. Dysostosis acrofacialis (synonymous with dysostosis otomandibularis, rodent syndrome), which has no ocular symptoms, must also be distinguished. In addition, middle ear malformations can also occur in craniofacial dysostoses such as dysostosis craniofacialis (Crouzon syndrome) or acrocephalosyndactyly (Apert syndrome), as well as in malformation syndromes with spinal malformations such as Klippel-Feil syndrome or Wildervanck syndrome. In addition, cases of malformations of the middle ear and external ear have been described as an adverse event when taking certain medications during pregnancy, e. g. in the context of thalidomide (Contergan®) embryopathy [13].

Apart from aesthetic aspects, the treatment of deformities consists of functional rehabilitation of the hearing. This can be achieved by hearing aids, by surgical means or in combination. The decision on therapeutic options depends on the age of the patient and the severity of the malformation. The age of the patient has an influence on the maturity of the auditory system and thus the ability to benefit from (bilateral) stimulation. The severity of the malformation limits the type of auditory rehabilitation [14]. Intraoperatively, a slit-like anatomy of the middle ear with little pneumatisation and only rudimentary ossicles may be found (hammer-anvil conglomerate) [15]. Reconstructive surgery is usually limited to patients with favourable anatomical conditions or mild cases where otoplasty can be performed in combination with ossiculoplasty [14]. Active middle ear implants offer a suitable alternative [16]. In severe malformations of the temporal bone, the risk of implantation of an active middle ear implant may be particularly high, for example due to a forward displacement of the facial nerve in the tympanomastoid course or accompanying vascular anomalies (see subsequent section), so that bone conduction hearing systems are preferred [14, 15].

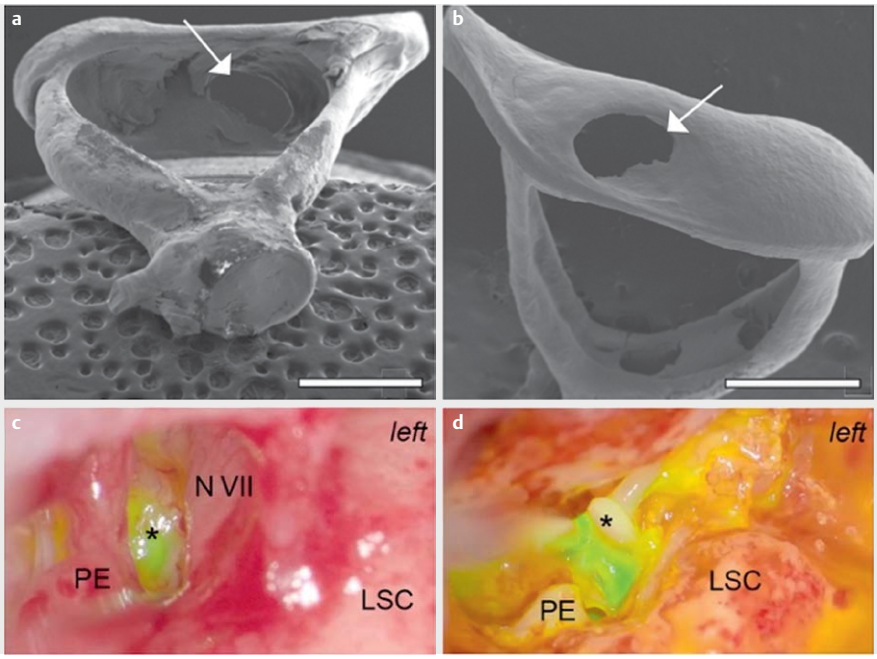
Clinical example: congenital stapes footplate defect

From a developmental point of view, the malleus and incus arise from the cartilage of the first pharyngeal arch, while the stapes superstructure arises from cartilage of the second pharyngeal arch. Like the annular ligament, the stapes footplate arises from the otic capsule. Here, the central footplate as well as the stapes superstructure arise from the neural crest during embryogenesis [17], while the outer part of the stapes footplate and the annular ligament are of mesodermal origin. Dysplasia of the inner ear is often associated with a malformed otic capsule, which may lead to congenital weakness or fistula formation in the stapes footplate or annular ligament. In addition, pressure fluctuations in the cerebrospinal fluid (CSF) can lead to thinning of the stapes footplate or tears in the annular ligament. As a result, patients with inner ear dysplasia are more prone to oto- or rhinoliquorrhoea following trauma or barotrauma, with an associated risk of vertigo, deafness and recurrent otogenic meningitis (▶ **Fig. 2**) [18–20].

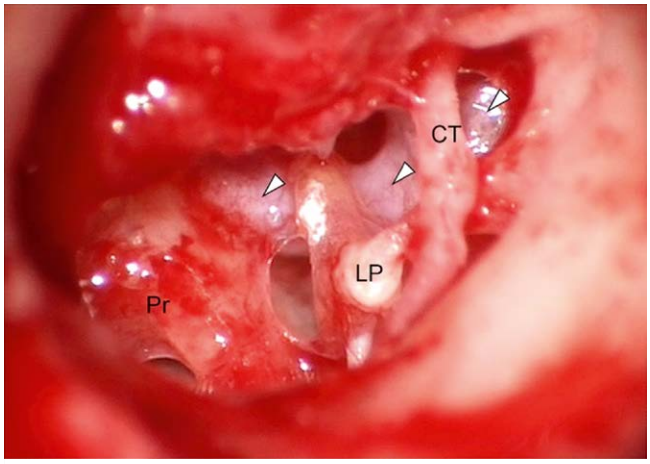
2.2 Vascular anomalies of the temporal bone

Advancement of the sigmoid sinus, protrusion of the bulbus venae jugularis or the internal carotid artery can lead to problems in the surgical management of minor and major ear malformations. This plays a role in the creation of a new auditory canal, in ossiculoplasty or in implantable hearing aid surgery [1, 7, 15, 21]. Furthermore, an stapedial artery that has not regressed (▶ **Fig. 3**) can lead to complications during surgery. In cases of malformation, the stapedial artery is present in up to 1:5,000 to 1:10,000 cases [22]. Ligation can lead to central reduced perfusion and injury to life-threatening bleeding [23].

Furthermore, vascular anomalies must be considered in the differential diagnosis of a pulse-synchronous tinnitus. Anomalies of the jugular bulb, the sigmoid sinus, the internal carotid artery as well as arteriovenous fistulas and malformations are possible [24]. In most malformations, tinnitus can also be audible to the examiner [25]. In the case of a venous malformation, tinnitus is more often perceived on the right side, as the size of the right jugular vein



▶ **Fig. 2** Congenital stapes footplate defect of the left ear in a 20-month-old boy with bilateral temporal bone malformation (cochlear aplasia on the right, incomplete partition type I on the left). Due to minor trauma, the stapes foot plate malformation on the left side led to oto-rhino-liquorrhea and finally to the diagnosis. **a–b** Electron microscope image of the congenital stapes foot plate defect (arrow). Scale bar: 1 mm. **c–d** Intraoperative visualisation of the perforation in the stapes footplate (asterisk) with intrathecal fluorescein application. **c** View of the stapes in situ shows fluorescein-labelled CSF leakage through the stapes footplate. **d** When the stapes is removed, CSF leakage occurs from the oval window. **LSC:** lateral semicircular canal; **NVII:** facial nerve; **PE:** pyramidal eminence. Fig modified after [20].



▶ **Fig. 3** Intraoperative tympanoscopic view of a persistent stapedial artery in a 20-year-old patient with conductive hearing loss of the left ear. The persistent stapedial artery passes under the anterior limb of the stapes (white arrowheads). **LP:** lenticular process, **Pr:** promontory, **CT:** chorda tympani, white arrowheads: Stapedia artery.

usually dominates over the left [26]. A high-riding jugular bulb may cause conductive hearing loss in addition to vertigo and tinnitus [27–29]. These symptoms arise either from direct contact with the ossicles or from invasion of the bony labyrinth, causing a third window lesion (with conductive hearing loss of the inner ear) [29, 30]. An aberrant internal carotid artery is is caused by maldevelopment during embryogenesis. Otoscopy reveals a reddish pulsating mass behind the tympanic membrane resembling a paraganglioma of the glomus tympanicum. The diagnosis of the respective anomalies is made by a combination of CT/MR angiography and diagnostic digital subtraction angiography [25], which is commonly indicated in every case of pulsatile tinnitus. CT can also provide information on the bony coverage of the vascular structures [31–33]. Treatment depends on the severity and subjective impairment. Arterio-venous fistulas are associated with a substantial risk for apoplexy, epilepsy or cerebral haemorrhage [34]. Treatment options include interventional radiological embolization, neurosurgical resection or radiotherapy, symptomatic drug therapy and clinical radiological follow-up [35, 36]. In the case of venous malformations, ligation can be performed [25].

3 Diseases of the Bone

3.1 Paget's disease (osteodystrophia deformans, osteitis deformans, Paget's syndrome)

The disease was first described by Czerny in 1873 and was called "osteitis deformans". The disease received its name from Sir James Paget [37, 38]. The aetiology is unknown and there is still no reliable evidence that the cause of the disease is of inflammatory origin. Infectious causes such as syphilis infection and paramyxoviruses [39], endocrine dysfunction, autoimmune causes, vascular lesions, inflammatory causes and hereditary factors are discussed [40]. Several gene loci have been associated with Paget's disease. Among others, a mutation has been described in the *SQSTM1* gene, which encodes the sequestome-1 protein [41]. This is an autophagosome-cargo protein that binds other proteins for selective auto-

phagocytosis. The disease affects men and women equally, with an incidence of up to 3 % at the age of 40 years and increases in prevalence with increasing age (up to 10 % in 90-year-olds) [42, 43]. Apart from osteoporosis, Paget's disease, which is diagnosed in only about 30 % of cases during life, is the second most common disease of the bone. Involvement of the middle ear in Paget's disease is rare with an estimated prevalence of temporal bone involvement of up to 1 % in Caucasian adults [44]. Paget's disease does not always cause deformities of the limb bones, as the term "osteitis deformans" may suggest. About one third of patients are symptom-free. Possible symptoms are bone pain, bending or shortening of the legs ("saber tibia") or an increase in the circumference of the head.

Typically, there is a phasic course, which in the first stage is associated with an increased vascularization and fibrous re-modelling of the bone due to a stimulation of bone resorption (osteolytic phase). In the second stage (mixed phase), there is excessive bone accretion. The third, osteoblastic phase is characterized by increasing de-vascularization. This results in a distended, less stable bone with an increased tendency to fractures. In the middle ear, microfractures may affect the stapes footplate (▶ **Fig. 4** a-c) [45]. In the fourth stage, there is a slow re-modelling process into an almost normal-looking lamellar bone. This last stage is predominantly found in subclinical cases with cranial involvement and therefore exclusively histologically. The disease most commonly affects the pelvis, femur and tibia. Rarely, there is involvement of the ossicles [46], for example manifesting with stapes fixation [47]. The clinical symptoms of middle ear involvement are characterized by unremarkable ear microscopic findings, conductive or mixed hearing loss and absent stapedius reflexes [44]. However, conductive hearing loss is not associated with ossicular re-modelling [48]. Besides an involvement of the ossicles and bone in the epitympanic or oval window, possible explanations for the conductive component include ear canal narrowing, fibrosis of the tympanic membrane, calcifications in the annulus fibrosus of the tympanic membrane, atrophy of the tympanic membrane, narrowing of the Eustachian tube or tympanofibrosis [46]. However, such changes are not reliably detectable histologically [49]. It is also discussed that the hearing loss can be explained by changes in bone density, mass and shape, which lead to an attenuation of the fine mechanics in signal transmission [49]. Monsell et al. described a correlation between the bone density of the cochlear capsule and the air conduction threshold as well as the sound conduction component [50, 51]. Merchant and Rosowski examined eight temporal bones of patients with Paget's disease using laser Doppler vibrometry. In three cases, they found a relative hypermobility of the umbo that has also been demonstrated in cases of dehiscence of the superior semicircular canal [27]. Furthermore, multiple microfractures of the otic capsule were observed in all 8 cases. Consequently, it is assumed that the acoustic energy is diverted away from the cochlea by the fractures that constitute a third window lesion and thus lead to a conductive hearing loss of the inner ear [27, 52]. Due the presence of conductive hearing loss, there is a risk of misdiagnosing Paget's disease as otosclerosis with the risk of unsuccessful surgical treatment [47].

The diagnosis of Paget's disease includes pure tone audiometry and stapedius reflexes in the case of middle ear involvement, as well as laboratory diagnostics, which show an elevated alkaline phosphatase. Conventional x-rays show osteolysis in early manifestations. Computed tomography (CT) may show bone thickening in the temporal bone, displacement of the internal carotid artery, widening of the mastoid with reduction of pneumatization, narrowing of the internal auditory canal and, very rarely, nerve compression [53]. More frequently, a widening of the internal auditory canal is described due to the growth of the mastoid [45, 48]. Scintigraphy shows an increased technetium-99m uptake in the affected bone and may be a useful addition to the radiological examinations. A biopsy of the affected bone can contribute to a histological confirmation of the disease.

The treatment of Paget's disease consists of inhibiting osteoclast activity with bisphosphonates, which can prevent the deformity. Analgesics are also used. Further treatment is symptomatic by treating the fractures (▶ **Fig. 5**), by the supplementation of calcium and vitamin D, and by physiotherapy.

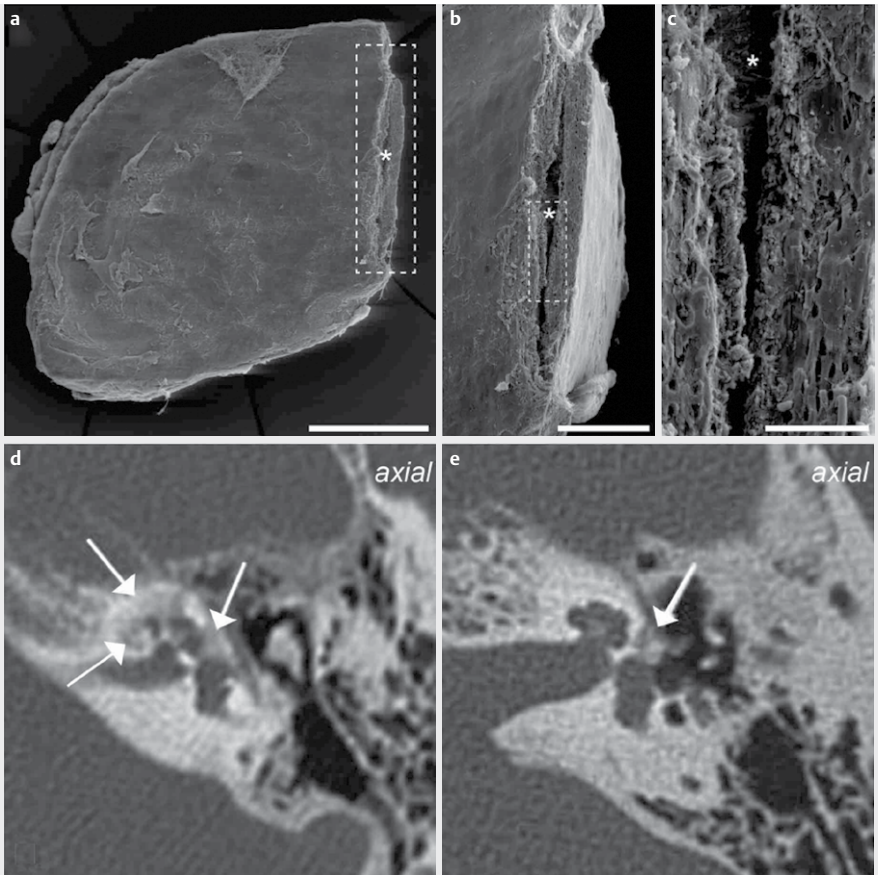
Paget's disease can manifest in the middle ear and mastoid, leading to conductive hearing loss (most likely localized in the inner ear). However, treatment is systemic. In patients with conductive hearing loss and other clinical indications of Paget's disease, imaging (▶ **Fig. 4 d–e**) may be helpful to differentiate the disease from otosclerosis and to avoid surgical treatment by ossiculoplasty, which is not considered to be a successful treatment option in Paget's disease [47, 54].

3.2 Osteogenesis imperfecta

Osteogenesis imperfecta (OI) is a genetic disease of connective tissue that is characterized by fragile, fracture-prone bone. A gene mutation of one of the two type I collagen genes (*COL1A1* or *COL1A2*) is described in 80 % to 90 % of the patients.

OI is classified into 4 types according to clinical manifestation, radiological criteria and pattern of inheritance [55, 56]: OI type I is inherited in an autosomal dominant pattern. It is the mildest form. Clinically, it is characterized by blue sclerae, non-deforming fractures and a normal body size. Hearing loss may occur in 50 % of the cases. OI type II is the most severe form, associated with multiple fractures in utero and is often resulting in stillbirth. OI type II is either transmitted in an autosomal dominant fashion or results from a sporadic new mutation. OI type III manifests with frequent fractures and progressive bone deformity from childhood on. Initially there are bluish sclerae, later they are white. Hearing loss is present in 50 % of cases. In addition, kyphoscoliosis, weak joints, funnel chest, dental changes and small accessory bones within the cranial sutures may occur. Inheritance is autosomal dominant or recessive. The pattern of inheritance of OI type IV is autosomal dominant. Clinically, it resembles OI type I, but is associated with white sclerae. Hearing loss is present in only 10–30 % of cases.

Otological symptoms are most commonly observed in OI type I, with hearing loss being most relevant. It may occur as conductive hearing loss or a combined hearing loss, which is mostly due to bone re-modelling processes at the stapes that may resemble otosclerosis. Intraoperatively, soft, calcareous thickening of the stapes footplate, vascularized bone in the oval niche covered by vascularized periosteum, fibrous degeneration of the stapes suprastructure and osteoporotic fixation of the footplate similar to otosclerosis are described [57–60]. Surgical hearing rehabilitation by



▶ **Fig. 4** **a-c** Electron microscope image of a stapes footplate fracture. Figure modified from [323]. a One part of the footplate is turned downwards, showing a fracture gap (asterisk). Scale bar: 500 µm. Dotted region shown in **b**. **b** View of the fracture gap (asterisk). Scale bar: 200 µm. Dotted region shown in **c**. **c** Magnified view of the fracture gap. Scale bar: 50µm. **d**-**e** CT morphological distinction between Paget's disease and otosclerosis. **d** Paget's disease shows remodelling processes within the cochlea (arrows). **e** Fenestral otosclerosis shows plaques in the fissula ante fenestram with a mixed otospongiotic-otosclerotic phase (arrow). Figure **d-e** modified after [54] (Courtesy of S. Kösling, Institute of Radiology, University Hospital Halle (Saale)).

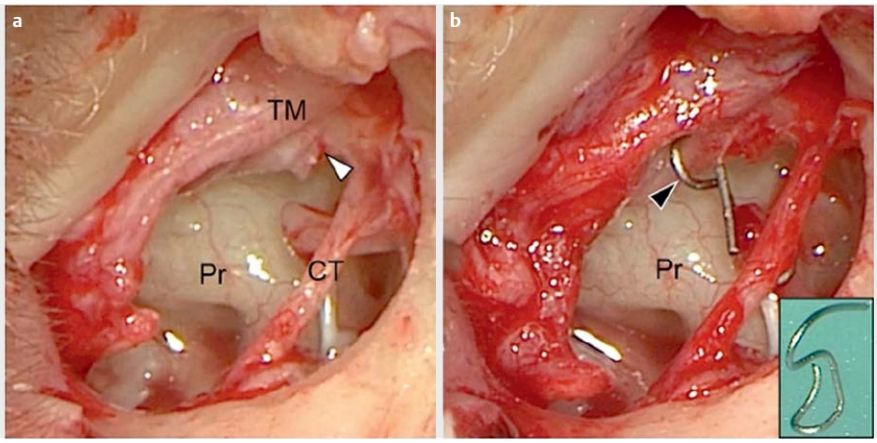
stapedotomy is possible, but is considered to be surgically challenging due to soft porous bone and the risk of a floating footplate [57–59]. Other general treatment approaches include the treatment of fractures, orthoses, physiotherapy and bisphosphonates as an inhibitor of bone resorption. New approaches include bone marrow transplantation [61, 62], intrauterine stem cell implantation [63], growth factors [64] and antibody therapy [65, 66].

3.3 Fibrous dysplasia

Fibrous dysplasia was first described by Weil [67]. It is a chronic, slowly progressive disease that may also occur in the context of Albright syndrome with bony lesions, abnormal pigmentation ("café-au-lait spots"), endocrine dysfunction and pubertas praecox [68]. Histologically, the disease is characterized by resorption of bone and fibrous re-modelling into stroma, as well as bony lesions from immature mesenchymal osteoblastic progenitor cells. These are caused by a non-heritable activating mutation in the α-subunit gene of the stimulatory G-protein coding gene. Consequently, there is an increase in cyclic adenosine monophosphate, which leads, among other effects, to the pathological bone lesions by activation of numerous protein kinases [69, 70].

The disease becomes symptomatic during childhood. A distinction is made between the monoostotic and the poliostotic type. The poliostotic type is progressive throughout lifetime and usually involves the long bones. The skull bone is affected in over 50 % of cases. The monoostotic type is the more common variant and often disappears at puberty. It involves the long bones, facial bones and membranous bones. Sarcomatous degeneration of the bone lesions is possible [71–73]. The prevalence is about 2.5 % [74]. Due to frequent bone pain and a laboratory elevation of alkaline phosphatase, the clinical appearance of fibrous dysplasia may resemble hyperparathyroidism. For this reason, patients with fibrous dysplasia are frequently reported to have undergone frustrated surgical procedures under the suspicion of a parathyroid tumour [75]. Isolated fibrous dysplasia is distinguished from hyperparathyroidism by laboratory diagnostics (calcium, phosphate, alkaline phosphatase). Laboratory diagnostics show an elevated alkaline phosphatase, which occurs in 30 % in the poliostotic type. Calcium and phosphate, on the other hand, are usually normal in fibrous dysplasia.

There are more than 100 reported cases of fibrous dysplasia with temporal bone involvement in the literature. In 70 % of cases, the monoostotic type, in 23 % of cases the polyostotic form is descri-



▶ **Fig. 5** **a** Intraoperative view into the tympanic cavity in a 30-year-old female patient with conductive hearing loss after malleus handle fracture (white arrowhead). **TM:** tympanic membrane, **Pr:** promontory, **CT:** chorda tympani. **b** View after reconstruction of the ossicular chain by a malleostapediopexy (black arrowhead). Insertion bottom right: Malleostapediopexy prosthesis made of titanium wire.

bed and 7 % occurred in the context of McCune-Albright syndrome [48]. Clinically, temporal bone involvement may result in painless swelling of the mastoid, further bony deformities, pathological fractures and cranial nerve palsies. Progressive narrowing of the external auditory canal can lead to conductive hearing loss. It is the most common symptom of temporal bone fibrous dysplasia and is reported in 80 % of cases with temporal bone involvement. Misinterpretation as auditory canal exostoses is common. Intraoperatively, however, unlike exostoses, vascularized bone with a cancellous, coarse-grained consistency is seen. Involvement of the middle ear or Eustachian tube obstruction may also be an explanation of conductive hearing loss. Radiologically, there are radiolucent areas with soft roundish borders and sometimes radiopaque areas (▶ **Fig. 6**).

The general treatment of fibrous dysplasia consists of physiotherapy and treatment of the fractures. Surgical therapy only comes to use symptomatically or in terms of biopsy to confirm the diagnosis. Canaloplasty may be useful for the symptomatic treatment of conductive hearing loss or of recurrent otitis externa. Prior to surgical ablation of exostoses, CT may reveal evidence of fibrous dysplasia with areas that are partly radiolucent and partly radiopaque. Regular follow-up is necessary because of the risk of progressive narrowing of the facial canal and progressive hearing loss.

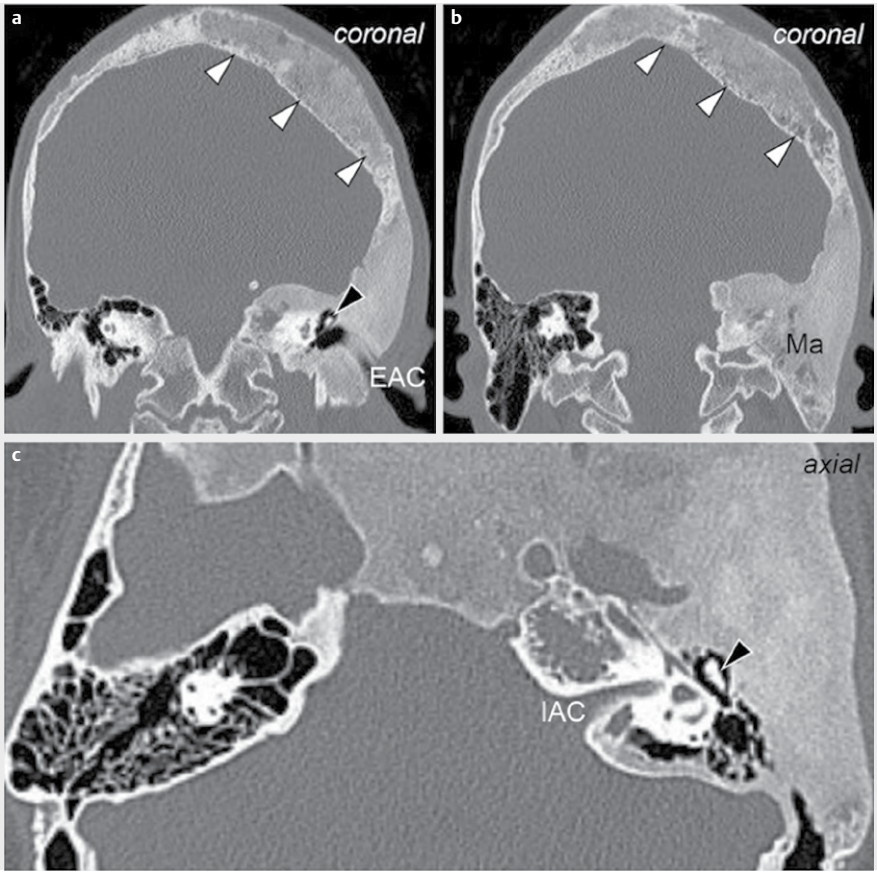
3.4 Osteopetrosis ("Albers-Schönberg syndrome", "marble bone disease")

Osteopetrosis manifests with a marked increase of bone density [76, 77], that is caused by defective osteoclasts and a resulting abnormal bone resorption. At the same time, there is an undisturbed osteoblast activity with increased formation of mineralized bone and cartilage. The prevalence is estimated at 1:20 000 [78]. There is defective resorption of calcified cartilage and primitive bone, resulting in the persistence of mineralized cartilage and primitive bone matrix, which prevents the maturation of bone. The disease exists as a dominantly inherited benign and recessively inherited malignant variant.

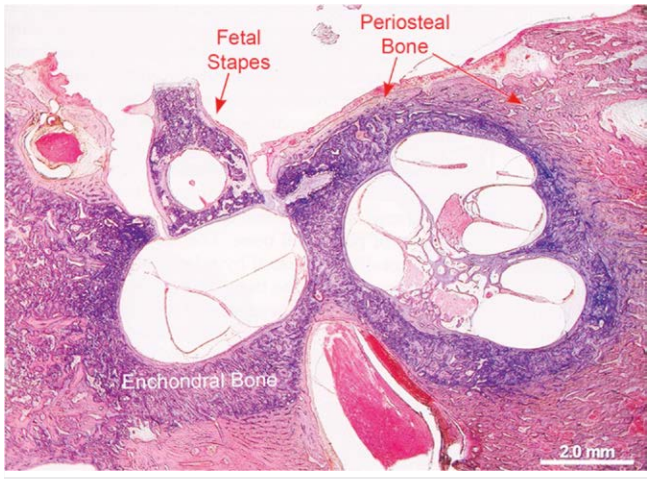
In the malignant type, osteopetrosis usually appears in childhood, is rapidly progressive and has a high mortality rate. In the majority of cases, malignant osteopetrosis is caused by a gene mutation in the *TCIRG1* gene [78], which encodes a subunit of the vacuolar proton pump. As a result of osteopetrosis, the bone marrow is repressed, leading to anaemia and thrombocytopenia. In addition, hepatosplenomegaly, an infectious tendency, narrowing of the neuroforamina with neurodegeneration, frontal protrusion, growth retardation, facial paresis, hearing and vision loss, fractures as well as mental retardation may occur. There is a significantly limited life expectancy (first to second decade of life). Histologically, the temporal bone shows dense, calcified bone of the labyrinth and ossicles [79], a non-pneumatized mastoid and a fetal stapes (▶ **Fig. 7**). Ear-specific symptoms may include recurrent otitis media, tympanic effusions, ear canal stenosis and conductive hearing loss [80, 81]. Bone marrow transplantation is used as therapy for the malignant type [82].

The benign type of osteopetrosis is usually asymptomatic. Affected patients have a normal life expectancy. It is caused by a gene mutation in the *CLCN7* gene, which encodes the α-subunit of the chloride transporter ClC-7 [76]. Osteopetrosis can lead to constriction of the cranial nerves due to cranial thickening (optic nerve, trigeminal nerve, vestibulocochlear nerve and facial nerve). Spontaneous facial nerve paresis with spontaneous recovery occurs as a frequent initial symptom. Consequently, in cases of defective recurrent facial pareses in young adulthood or childhood radiological imaging needs to be considered. In addition, attention should be paid to dental infections due to osteomyelitis, jaw thickening, intracranial venous congestion due to cranial thickening and a resulting increase in intracranial pressure, as well as cutaneous syndactyly, which often leads to the initial diagnosis.

Hearing loss can be caused by a narrowing of the middle ear space, by bony deposits in the oval niche and a resulting fixation of the auditory ossicles [83, 84]. Furthermore, constriction of the annulus fibrosus may lead to a loss of tension of the tympanic membrane and narrowing of the Eustachian tube may lead to tympanic effusion that may further cause conductive hearing loss [85]. With regard to facial paresis occurring in the context of osteopetrosis, therapeutic success has



▶ **Fig. 6** CT of the skull in a 23-year-old female patient with fibrous dysplasia. **a, b** The pathognomonic focal sclerotic ground-glass bone expansion with involvement of the cranial bone (white arrowheads), os zygomaticum, os sphenoidale and temporal bone on the left is shown. The external auditory canal **(EAC)** is narrowed. The malleus is properly configured (black arrowhead). The left mastoid **(Ma)** shows almost complete loss of pneumatization. **c** The internal auditory canal **(IAC)** is normally wide. There is a properly configured malleus and incus (black arrowhead) in a ventilated middle ear.



▶ **Fig. 7** Osteopetrosis of the temporal bone in an axial histopathological temporal bone section of a 15-month-old boy. The patient suffered from mental retardation and congenital bilateral deafness. The stapes shows a fetal shape, characterised by a thickening of the stapes legs and foot plate. The immature bone consists of a combination of calcified cartilage and thin trabeculae of lamellar bone. The immature bone is thickened and shows increased density. Figure and legend modified after [48].

been reported with complete intratemporal facial decompression [83, 86, 87]. In cases of increased intracranial pressure, decompressive craniotomy can lead to a reduction in intracranial pressure. Tympanoplasty may contribute to hearing improvement.

3.5 Langerhans cell histiocytosis

Langerhans cell histiocytosis is a neoplasia-like disease that leads to acute disseminated infiltrations of various organ systems and has a high mortality if left untreated. Langerhans cell histiocytosis is characterised by a proliferation of benign histiocytes and the accumulation of pathologically altered Langerhans cells occurs. Langerhans cells are inactive dendritic cells in the stratum spinosum of the epidermis that express CD1a, S100 protein and langerin [88, 89] and serve the antigen presentation. Langerhans cells belong to the mononuclear phagocytic system. The cause of Langerhans cell histiocytosis is most likely a proliferation of Langerhans cells due to immunological dysfunction. The incidence is between 1:200 000 and 1:2 000 000. Three subtypes of Langerhans cell histiocytosis are distinguished, that will be discussed below.

3.5.1 Unifocal eosinophilic granuloma

Eosinophilic granuloma usually occurs in young adults and children. It is the mildest form of the disease and results in solitary osteolytic lesions. Usually there is only skeletal involvement of the long tubular bones, ribs, vertebrae, skull, and also the mastoid. There may be small temporal bone lesions with possible auditory canal fistulae, otalgia, mastoid swelling, cranial nerve palsies due to bony lesions at the jugular foramen and otorrhoea. Treatment consists of local curettage and where appropriate of radiation [90, 91].

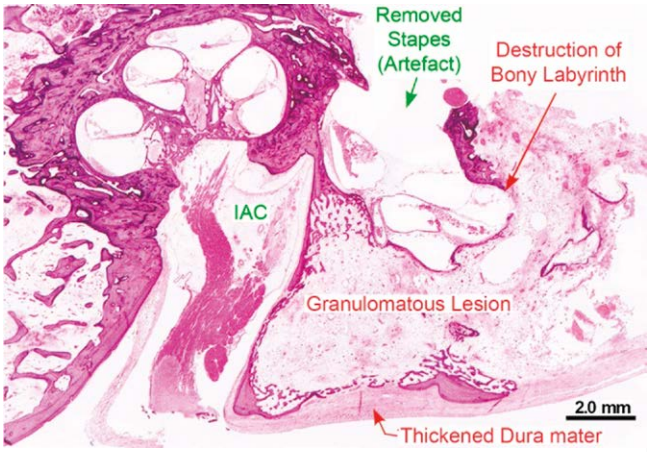
3.5.2 Hand-Schüller-Christian syndrome

Hand-Schüller-Christian syndrome occurs in children under the age of 5 years, rarely also in the second or third decade of life. In 15–30 %, the outcome is fatal. In contrast to eosinophilic granuloma, multifocal lesions in bones and organs (e. g. in the liver or spleen) with embedded histiocytes, cholesterol deposits and multinuclear cells are common. Extraskeletal manifestations of the skin, lymph nodes and organs are rare. Systemic symptoms include fever, recurrent upper respiratory tract infections, loss of appetite and lymph node swelling. Clinical symptoms in the ear may mimic acute or chronic otitis media. The diagnosis is made by biopsy and the detection of histiocytes. Occasionally, spontaneous regression occurs. Treatment consists of low-dose chemotherapy under the aim of systemic symptom control.

3.5.3 Letterer-Siwe syndrome

Letterer-Siwe syndrome is a disseminated, rapidly progressing type of the disease, usually occurring in children under the age of three years. It leads to a diffuse organ involvement. Hepatosplenomegaly, lymph node swelling, anaemia, skin rash and skeletal lesions (especially of the skull) may occur. The course of the disease is acutely febrile and is associated with a poor prognosis and a high mortality rate [92]. Treatment consists of corticosteroids, cytotoxic substances such as methotrexate, vincristine and cyclophosphamide. Radiation, bone marrow transplantation or stem cell transplantation [93] are also available. In case of survival, there are permanent stigmata such as short stature, diabetes insipidus, exophthalmos, pulmonary fibrosis and vertebral body compression. In up to 25 % of cases, there are destructive bone lesions with calvarial defects. These may involve the temporal bone and lead to otological symptoms. Initially, the disease often manifests in the external, middle and/or inner ear with the appearance of granulation tissue, polyps, otorrhoea, retroauricular swelling, vertigo, hearing loss and occasionally a positive fistula sign [94–101]. Because of its similarity to chronic otitis media, frequent mastoid surgery prior to correct diagnosis has been reported in the literature [95, 96, 102, 103]. Bone destructions are found on temporal bone CT [95, 96, 104]. The diagnosis is confirmed by deep biopsy from the lesion (▶ **Fig. 8**) [105].

In summary, all forms of Langerhans cell histiocytosis can lead to an inflammatory disease pattern. Consequently, in case of CT-morphologically bilateral destructive ear disease associated with increased erythrocyte sedimentation rate and without other evidence of infection, or in cases of long-term granulation tissue after ear surgery with persistent otorrhoea and skin lesions or auditory canal fistulas, Langerhans cell histiocytosis needs be considered as a differential diagnosis and a biopsy has to be performed.



▶ **Fig. 8** Langerhans cell histiocytosis (Letterer-Siwe disease) in an axial histopathological section of the temporal bone of a 23-month-old child with bilateral otorrhoea. The diagnosis of Langerhans cell histiocytosis was made by biopsy of the auditory canal. Histology showed destructive granulomatous lesions in the mastoid and bony labyrinth and a thickened dura mater. The missing stapes is considered to be an artefact. **IAC**: internal auditory canal. Figure and legend modified after [48].

3.6 Proteus syndrome

Proteus syndrome causes a growth of skin, bones, muscles, fatty tissue, blood and lymph vessels. The cause of the disease is unknown. Mutations in the *AKT1* and *PTEN* genes or somatic mutations are discussed as possible causes. At birth, affected persons usually have no obvious stigmata. However, patients are at increased risk of developing tumours such as unilateral ovarian cystadenomas, testicular tumours, meningiomas and adenomas of the salivary glands. The disease can lead to bone growths on the mastoid and thus to ear canal obstruction, similar to ear canal exostoses. Surgical widening of the auditory canal may be indicated to improve hearing. Intraoperatively, the exostosis-like bone growths do not appear as compact bone, but as aerated mastoid cells or similar to the consistency of fibrous dysplasia.

4 Autoimmune Diseases

4.1 Granulomatosis with polyangiitis

In granulomatosis with polyangiitis (formerly Wegener's disease/granulomatosis), necrotising granulomas occur in the upper and lower respiratory tract, in the kidney and rarely in other organs. Otolaryngologic manifestations of this systemic vasculitis may occur as recurrent sinusitis, headaches, rhinorrhoea or (bilateral) otitis media. Laboratory findings include normochromic, normocytic anaemia, thrombocytosis, positive rheumatoid factors, hyperglobulinaemia (IgA) and anti-neutrophil cytoplasmic antibodies (c-ANCA). Furthermore, there is an increased erythrocyte sedimentation rate. The cause of the disease is not fully understood, although an immune-mediated disorder is suspected. In this case, tis-

sue destruction occurs as a result of an inflammatory disease pattern with a subsequent immune response including production of c-ANCA, which cause cell damage by an interaction of neutrophils and mucosal tissue [106]. The diagnosis is confirmed by histology with repeated biopsies and the combination of clinical appearance and the detection of c-ANCA in the blood. Cellular necrosis and inflammatory granulomas with multinucleated giant cells, vasculitis and microabscesses may be found [48]. The disease can affect the mastoid, middle ear, tympanic membrane. If the Eustachian tube is affected, the symptoms resemble those of otitis media with effusion. Furthermore, facial paresis [107] or sensorineural hearing loss may occur [108, 109]. Occurrence in the middle ear may be associated with destruction of the round window, the Fallopian canal and the inner ear [110, 111]. Therapy consists of immunosuppressants and steroids, that may lead to a remission of hearing loss [112]. If left untreated, the disease is fatal in 90 % of cases.

Consequently, especially in bilateral, recurrent or protracted otitis media, an autoimmunological disease should be considered and c-ANCA should be sought. Surgical treatment should be carefully indicated in granulomatosis with polyangiitis due to the risk of protracted healing [113].

4.2 Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Eosinophilic granulomatosis with polyangiitis is another type of systemic vasculitis. The leading symptoms include a pulmonary manifestation with severe allergic asthma attacks. A manifestation in the middle ear and mastoid is rare and can lead to the symptoms of acute otitis media, mastoiditis or chronic granulating otitis media [114, 115]. Conventional treatment using antibiotics and myringotomy is often unsuccessful in eosinophilic granulomatosis with polyangiitis. The detection of perinuclear antibodies (p-ANCA) is the guiding factor. Therapy consists of steroids [116].

4.3 Recurrent polychondritis (relapsing polychondritis)

Recurrent polychondritis was first described in 1923 by Jaksch-Wartenhorst [117]. This disease of unknown origin is characterized by recurrent inflammatory reactions of the cartilage. In addition to the auricle and auditory canal, the eye, cardiovascular system, kidney and nervous system can also be affected. There are associations with other autoimmune diseases. It is suspected that the disease is caused by an autoimmune reaction to connective tissue and epitopes that occurs as the result of the failure of regulatory factors [118, 119]. A unilateral or bilateral inflammation of the auricle is typical, but the cartilaginous ear canal can also be affected and thus resemble diffuse acute otitis externa [120]. An occlusion of the Eustachian tube can also lead to acute otitis media with effusion. The diagnosis is made according to clinical criteria and needs be considered in the presence of bilateral infections of the auricle, especially in combination with non-erosive, seronegative polyarthritis, nasal cartilaginous inflammation, ocular inflammation (conjunctivitis, keratitis, scleritis, uveitis), respiratory tract cartilage inflammation (laryngeal or tracheal cartilage) and vestibulocochlear dysfunction [121]. Treatment consists of immunosuppressants and steroids.

4.4 Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory autoimmune disease. Its cause is not yet completely understood. A genetic predisposition is suspected, which leads to an increased immune reaction to an initial infection. In 1989, Hoffman et al. described the case of a 69-year-old female patient with rheumatoid arthritis and involvement of the middle ear and mastoid, who showed the clinical symptoms of chronic otitis media and resulted in facial paresis [122]. Gussen et al. report the case of a 55-year-old female patient with involvement of the malleo-incudial joint [123]. In histopathology, a thickened tympanic membrane and fibrous remodelling of the ossicular chain as well as demineralization of the malleus and incus are described in rare cases [124]. Consequently, the picture of acute otitis media and possibly facial paresis in patients with rheumatoid arthritis may indicate an acute episode of the underlying disease and requires a joint therapy concept together with rheumatology.

5 Neoplasms

Various neoplasms can manifest in the middle ear and lateral skull base. The patient's history (e. g. pulse-synchronous tinnitus of the ear, known neoplastic diseases in the history, drug use, syndromal diseases) may provide initial hints for their origin. Depending on the findings, the diagnosis can be further confirmed by additional diagnostics (e. g. radiological imaging) and by biopsy. Treatment depends on the entity and symptoms and usually consists of either surgical resection, medical therapy, radiotherapy or a combination.

5.1 Neoplasms of the haematopoietic system

Diseases of the blood and haematopoietic system can be grouped into the following four subcategories [125, 126].

1. Myeloid neoplasms, which originate from the progenitor cells in the bone marrow, that usually develops erythrocytes, granulocytes, monocytes and megakaryocytes. These are further subdivided into acute myeloid leukaemia, myeloproliferative neoplasms (chronic myeloid leukaemia, polycythaemia vera, essential thrombocytopenia) and myelodysplastic syndromes.
2. Lymphoid neoplasms arise from the progenitor cells of lymphocytes or mature lymphocytes. Historically, they have been further subdivided into lymphoid neoplasms with bone marrow and blood involvement (leukaemia) and lymphoma masses. However, they are not always distinguished with certainty. A more common classification is B-cell, T-cell or natural killer (NK) cell lymphoma. Hodgkin's lymphoma represents another subcategory and originates from the germ cells of the B cells.
3. Neoplasms with myeloid and lymphoid components, e. g. acute leukaemia.
4. Histiocytic/dendritic neoplasms (e. g. histiocytic sarcoma) originating from the dendritic cells or histiocytes.

Since the majority of the literature describing the occurrence of haematological diseases in the ear was published before the publication of the classification cited above, an older terminology (leukaemia, lymphoma, myeloma) will be used here.

5.1.1 Leukaemia of the temporal bone

Leukaemia of the temporal bone is histologically characterized by diffuse infiltration, haemorrhage and remodelling of the mastoid bone (especially the petrous apex) by leukaemia cells (▶ **Fig. 9**) [127–130]. The tympanic membrane and mucosa of the middle ear may be thickened by leukaemic infiltrates and exhibit an inflammatory exudate. Secondary infections are common.

A special type is granulocytic sarcoma, which is an extramedullary accumulation of immature cells with myeloid differentiation outside the bone marrow. Symptoms, that are primarily due to growth, include aural fullness, otalgia, otorrhoea and facial paresis. The symptoms resemble those of acute otitis media [131]. Diagnosis includes CT, that may show bony destructions, and magnetic resonance imaging (MRI), that shows a signal enhancement in the corresponding lesions after contrast administration.

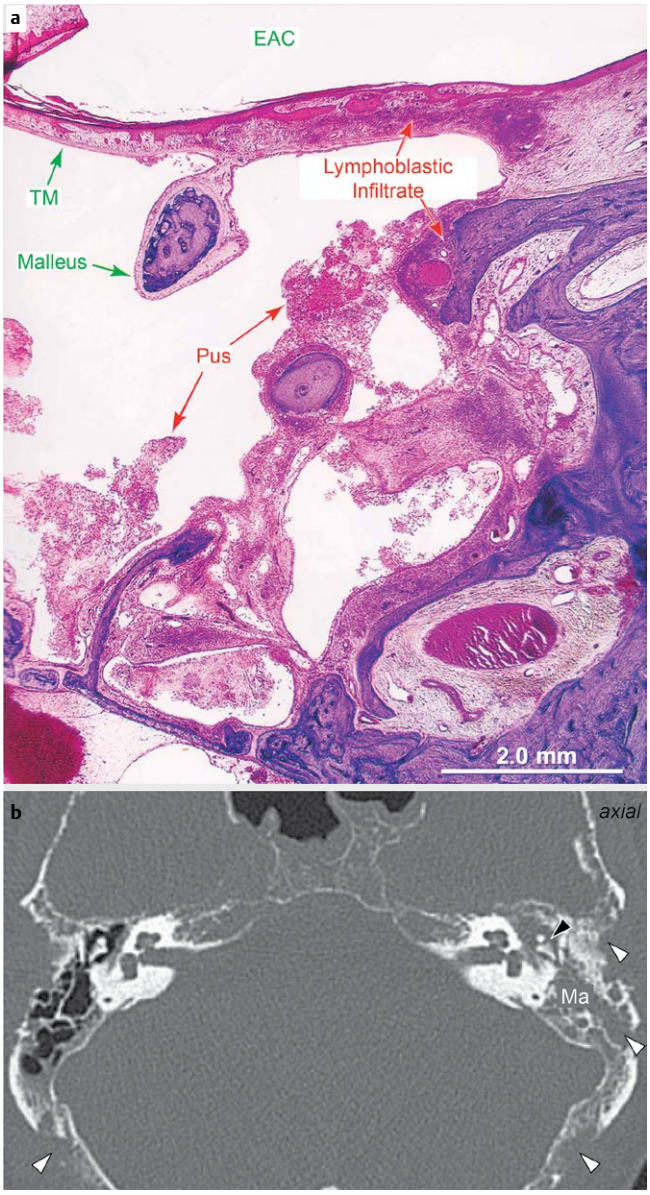
5.1.2 Myeloma of the temporal bone

Myeloma of the temporal bone corresponds to B-cell non-Hodgkin lymphoma (category 2) and can affect all bones of the body, predominantly the spine and long tubular bones. It usually occurs between the age of 40 and 60. The temporal bone usually is affected in the terminal stage only. Histologically, the bone is replaced by plasma cells (myeloma cells). The symptoms may also resemble acute otitis media [132], but are usually overshadowed by the disease's manifestation at other sites.

Diseases of the blood and haematopoietic system may lead to an initial manifestation in the middle ear and mastoid and resemble acute otitis media or skin ulcer due to otorrhoea and mastoid swelling [156]. Due to the possible aggressive course of the disease, an early diagnosis and initiation of chemotherapy is necessary.

5.2 Malignant epithelial neoplasms

Malignant epithelial neoplasms of the ear originate in the auricle in 60 %, in the auditory canal in 28 %, and in the middle ear or mastoid in 12 % [133]. The incidence ranges from 1:4 000 to 1:20 000. Malignant epithelial neoplasms occurring in the middle ear have a worse prognosis than those occurring in the ear canal or pinna [133, 134]. Two thirds of malignant epithelial neoplasms of the auricle are basal cell carcinomas, one third are squamous cell carcinomas. In the middle ear, the distribution is reversed with two-thirds squamous cell carcinomas and only one-third basal cell carcinomas. There are almost exclusively case reports reporting on the occurrence of malignant melanoma in the middle ear. In 11 % of cases, lymphogenic metastasis is already evident at initial diagnosis [133]. Malignant melanoma has an extremely poor prognosis with a metastasis rate of around 50 % [135]. Possible symptoms include otorrhoea, hearing loss and pain [135]. In addition, facial paresis, dizziness and mastoid erythema or swelling may occur [133, 136]. Radiation has been reported to be a risk factor for the occurrence of malignant epithelial tumours of the middle ear [137–140]. The diagnosis is confirmed by biopsy or excision. Therapy usually consists of surgical resection. In cases of middle ear involvement, an additional subtotal petrosectomy has to be performed.



▶ **Fig. 9** **a** Acute lymphocytic leukaemia in an axial histopathological section of the right temporal bone of a 9-year-old boy. Clinically, there was otalgia, a hyperperfused right tympanic membrane and mastoid swelling. The histopathological section showed lymphoblastic infiltrates, oedematous thickening and hypervascularisation of the tympanic membrane and the middle ear mucosa. Furthermore, pus was found in the middle ear. EAC: external auditory canal. TM: tympanic membrane. Figure and legend modified after [48]. **b** Axial CT of the temporal bone of a 55-year-old male adult with B-cell chronic lymphocytic leukaemia (B-CLL). Bony destruction of the calvarial bone and left mastoid (white arrowheads) with complete obstruction of the aerated mastoid cells is seen. **Ma:** mastoid; black arrowhead: incudo-malleal joint.

5.3 Glandular neoplasms

The leading symptoms of benign glandular neoplasms include painless swelling and hearing loss; malignant neoplasms may cause otorrhoea and nerve paresis. Four entities of glandular neoplasms

are distinguished according to Dehner and Chen [141]. Murphy et al. described carcinoid of the middle ear in 1980 [142].

5.3.1 Adenoma

Adenomas can originate from the apocrine glands of the auditory canal, usually the ceruminal glands. This is why the term ceruminoma was formerly used. However, other glandular tissues such as the hair follicles or sebaceous glands are also possible origins of adenomas. Glands have a two-layered structure and consist of an oxyphilic layer on the inside and a myoepithelial layer on the outside. Consequently, glandular neoplasms may have a pleomorphic cell population of basal myoepithelial cells (which express cytokeratin types 5 and 6, S100 and the tumour protein p63) and luminal ceruminous cells, which express cytokeratin type 7 [143]. If the adenomas originate from the middle ear epithelium, light microscopy shows a mucus formed by the tumour in the cytoplasm or in the glandular lumen [144]. There are histological similarities of adenomas to mixed tumours or adenoid cystic carcinomas. An adenoma can be distinguished from carcinoma by the absence of bone erosion. Clinically, there is a mass in the middle ear or auditory canal, which has a slowly progressive growth that may be associated with a slow hearing loss. Rarely, facial paresis [145] or a pulse-synchronous ringing in the ears may occur [146].

5.3.2 Pleomorphic adenoma

Pleomorphic adenoma may occur in the outer ear canal and may initially be clinically apparent by swelling of the outer ear canal. It may arise from the ceruminal glands or, in rare cases, from ectopic salivary gland tissue [147–152]. Pleomorphic adenoma is histologically characterized by a heterogeneous histological pattern with myxoid portions in 90 %, pseudocartilaginous portions in 50 % and squamous portions in 25 % of cases [153].

5.3.3 Adenoid cystic carcinoma

Adenoid cystic carcinoma is a malignancy arising from the apocrine, seromucinous ceruminal gland tissue or salivary gland tissue that may occur in the ear canal. Symptoms include pain and swelling with a slow growth tendency. The carcinoma is prone to recurrence after surgical removal and to distant metastases. The recurrence rate is reported to be 41 % within an average interval of eight years [154]. Histology shows a "Swiss cheese pattern", which is characterized by cylinders with hollow centres and with embedded acidophilic mucous material. Differential diagnosis includes basal cell carcinoma, ceruminoma, mucoepidermoid carcinoma and adenocarcinoma [155].

5.3.4 Adenocarcinomas

Adenocarcinomas develop from glandular atypia of the ceruminal glands [156, 157] or sebaceous glands [158, 159] of the external auditory canal or middle ear epithelium [160–162]. Metastases of adenocarcinoma must be considered as a differential diagnosis.

5.3.5 Carcinoid of the middle ear

The carcinoid of the middle ear was first described in 1980 by Murphy et al [142]. The tumour originates from the neuroendocrine cells (so-called Kulchitsky cells), that are abundantly present in the pancreas, lungs and gastrointestinal tract and synthesize peptide hormones. Carcinoid of the middle ear most frequently affects adults, predominantly females [163]. Symptoms include conductive hearing loss and swelling or masses in the middle ear. A recurrence rate of 22 % has been reported. Metastases occur in up to 9 % of cases [163]. Histology shows a similar appearance as an adenoma. It is discussed that both adenoma and carcinoid of the middle ear are the same type of tumour with different degrees of glandular and neuroendocrine differentiation [164, 165].

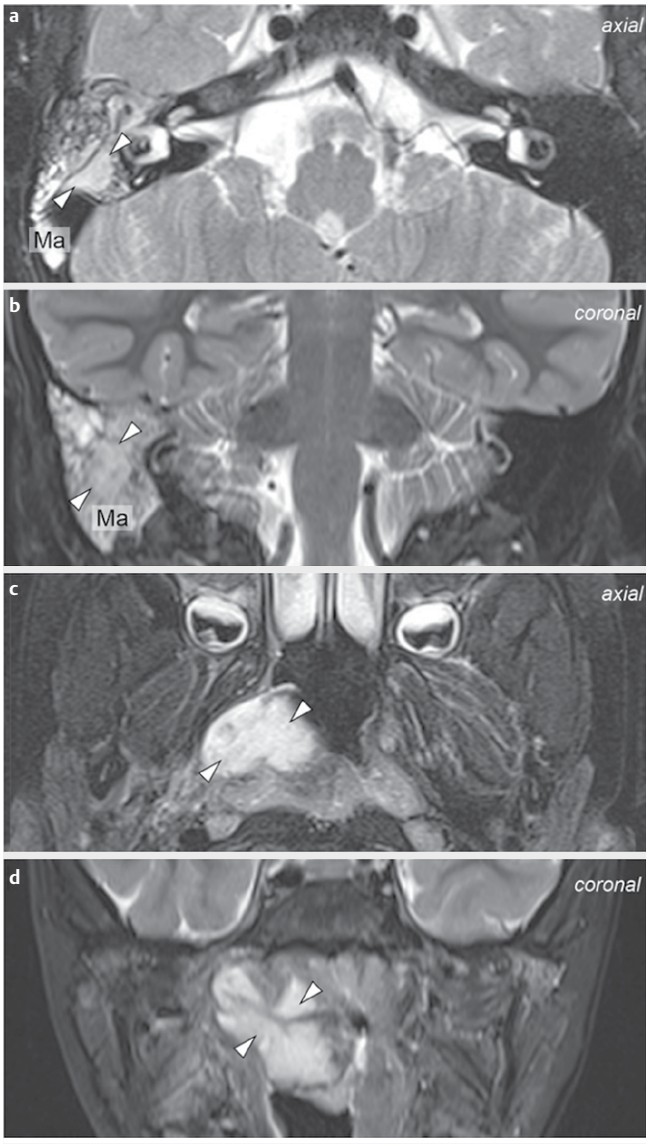
5.4 Sarcomas

5.4.1 Osteogenic sarcoma

Osteogenic sarcoma is the most common malignant neoplasm of bone and occurs in approximately 75 % of patients between the ages of 10 and 25. It may occur in children as part of retinoblastoma, Li-Fraumeni syndrome, Rothmund-Thomson syndrome or Werners syndrome [166]. In older adults, an association with Paget's disease or radiation has been described [167]. Osteogenic sarcoma originates from mesenchymal stem cells, that can differentiate into bone, connective tissue or cartilage. It is characterized by a malignant sarcomatous stroma with formation of osteoid (soft, non-mineralized bone) and bone. In 90 % of cases, the metaphyses of the long tubular bones are affected [168]. Occurrence in the temporal bone is very rare [138, 169–176]. The existing case reports suggest an association with radiation (e. g. nasopharyngeal carcinoma or paraganglioma). The prognosis of tumours induced by radiation is poor [138]. Symptoms include a slowly growing retroauricular swelling of a bony consistency that is displaceable towards the skin [174]. If present, this swelling may be painful and associated with otorrhoea [173].

5.4.2 Rhabdomyosarcoma

Rhabdomyosarcoma commonly affects children. It may manifest in the orbit, oral cavity, nose, pharynx or middle ear (▶ **Fig. 10**) [177, 178]. It usually occurs in the first decade of life, mainly below the age of five years [179]. If the middle ear is affected, the disease is almost always fatal [180, 181]. In addition to an extension into the mastoid tip and the middle cranial fossa, growth along the Fallopian canal and the internal auditory canal into the posterior cranial fossa is possible [182, 183]. Depending on the origin of rhabdomyosarcoma, histology reveals rhabdomyoblasts or striated muscle and positive immunostaining for muscle-specific proteins such as actin, myosin, desmin and myoglobulin is found. Electron microscopy shows myofilaments, Z-bands, desmin filaments. Four histological subgroups exist (embryonic, alveolar, botryoid, spindle cell). Symptoms include bloody otorrhoea, which may be erroneously interpreted as a sign of acute otitis media, and facial nerve palsy, which usually occurs in the later stages. Therapy usually consists of polychemotherapy, which should be carried out in certified oncological centres. In Germany, therapy is carried out after registration in the "Soft Tissue Sarcoma Registry" (SoTiSaR) according to the recommendation of the study centre. Surgical therapy is indicated only in exceptional cases and after assessment by a surgical reference centre for rhabdomyosarcomas. Surgery needs to be indicated with care under consideration of all possible functional deficits [179, 184, 185].



▶ **Fig. 10** T2-weighted fat-suppressed MRI images of a 5-year-old boy with an embryonal rhabdomyosarcoma of the right mastoid and epipharynx. A hyperintense signalling of the tumour (white arrowheads) with complete obstruction of the aerated mastoid cells is shown (**Ma, a**, **b**). The tumour (white arrowheads, **c**, **d**) extends into the epipharynx via the petrous apex.

5.4.3 Chondrosarcoma

Cartilage neoplasms account for up to 33 % of bone tumours. They are difficult to distinguish from chondromas [186]. Chondrosarcomas usually affect adults between the age of 25 and 50 years. Chondrosarcomas show a slow growth and an equal gender distribution. The clinical appearance is characterized by early pulmonary metastasis, rapid growth and osteolytic lesions as signs of malignancy [187, 188]. Involvement of the temporal bone is very rare and most likely occurs in the mastoid tip and clivus [189–191]. Symptoms include diplopia, headache, hearing loss, balance disorders, visual changes and hypaesthesia of the facial skin. Manifestation in the auditory canal is also possible [189, 192].

5.5 Paragangliomas of the temporal bone (tympanojugular paragangliomas)

The first description of vascular paragangliomas (formerly called “glomus tumours”; glomus = autonomic ganglion = paraganglion) was made 1941 by Guild [193]. Paragangliomas are the most common neoplasms of the middle ear [194] and originate from the parasympathetic ganglion cells. Two types of paragangliomas are described, “chromaffin” (epinephrine-producing) and non-“chromaffin” (non-epinephrine-producing) types [195]. Paragangliomas usually occur sporadically; a few are associated with hereditary syndromes, typically multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome or neurofibromatosis type 1 [196, 197]. In rare cases, they occur as multiple tumours [194, 198]. Hereditary paragangliomas are caused by germline mutations affecting the mitochondrial succinate dehydrogenase complex. Compared to sporadic paragangliomas, hereditary paragangliomas are more likely to occur as multiple tumours, to manifest at a younger age and to be associated with neuroendocrine tumours. As a consequence, genetic diagnosis is recommended in patients that present with paragangliomas [199]. The most common clinical manifestation combination consists of paraganglioma of the middle ear (tumour of the glomus tympanicum in the mesotympanum) and the ipsilateral carotid bifurcation (tumour of the glomus caroticum). Paragangliomas usually occur in middle-aged patients and women are affected more frequently than men [200]. The classification of tympano-jugular follows the classification according to Fisch [201]. Paraganglioma of the middle ear (Fisch type A) originates in the glomus tympanicum and is confined to the middle ear. Paragangliomas of the jugular fossa (originating from the glomus jugulare) but also paragangliomas of the vagal nerve (originating from the glomus vagale) may destroy the temporal bone. Fisch type D paragangliomas extend intracranially.

Symptoms include hearing loss in 91–100 % of cases [202, 203], pulsatile tinnitus in the ear in about 52 % of cases, otalgia in about 28 %, and vertigo in about 25 % of cases [203]. Clinical examination classically reveals a reddish pulsating mass behind the second and third tympanic quadrant (▶ **Video. 1**). Differential diagnoses include an elevated bulb of the jugular vein, an abnormal course of the internal carotid artery, a schwannoma in the jugular foramen, or plasmocytoma, meningioma or neurofibroma [204]. Paragangliomas of the jugular fossa can lead to lesions of the lower cranial nerves caused by compression. When growing into the aerated mastoid cells, an infiltration of the infralabyrinthine space may occur even before bone destruction is visible in radiological imaging [205]. Subsequently, bony destruction of the cochlea and vestibular labyrinth may occur [205]. The incidence of malignant paraganglioma is estimated to be approximately 1:4 000 000 people [206, 207]. Distant metastases in the context of malignant paragangliomas are rare and occur in up to 4 % of the cases. They may be present in the lungs, liver or lymph nodes [208]. Paragangliomas of the middle ear typically receive their vascular supply from the inferior tympanic artery and the ascending pharyngeal artery. Large tumours receive additional blood supply from the vertebral artery [209]. Diagnostics include MRI and angiography. T1-weighted MRI typically shows a so-called salt-and-pepper pattern due to the different flow velocities within a richly vascularized tumour (▶ **Fig. 11**) [210]. Functional imaging using radiotracers has a high

▶ **Video. 1**

sensitivity concerning the identification of paragangliomas [211]. It is indicated in patients under the age of 40 years, in cases of positive genetic testing, if there is a positive family history of paragangliomas or in cases of particularly large paragangliomas in order to exclude a multilocular occurrence or metastasis [212]. The therapy depends on the tumour size, the affected structures, the age at diagnosis, the hormone expression and other concomitant diseases. An indication for surgery usually is given in smaller tumours in which surgical resection can be carried out with function preservation. It is accompanied by prior embolization. In cases of inoperability, old age or severe concomitant diseases that increase the risk of surgery and postoperative morbidity, radiotherapy with good long-term results is available as an alternative [213–215]. In cases of multiple tumours or metastatic growth, radioreceptor therapy may also be indicated [216].

5.6 Metastases

Metastases occurring in the middle ear and mastoid may have their primary in the breast, kidney, lung, stomach, larynx, prostate, thyroid, cervix, liver, brain or skin [217, 218]. Since metastases in the middle ear usually occur late in the course of the disease, the symptoms are often overshadowed by the symptoms of the primary tumour or by other metastases. Temporal bone metastases resemble the histology of the primary tumour, but are often less differentiated [48]. Metastases may have osteolytic properties or stimulate bone proliferation. They usually grow destructively at the beginning but may also present with bone-repairing properties (e. g. mammary and prostate). Most commonly, temporal bone metastases occur in the petrous bone [217, 219]. Symptoms depend on the site of occurrence and size. Conductive hearing loss and pain may occur when the external auditory canal, middle ear, mastoid and auditory tube are affected. Meningeal carcinomatosis is a special form of carcinomatosis that spreads into the subarachnaoid space and the internal auditory canal and may consequently affect the cranial nerves and the inner ear.

5.7 Benign blood and lymphatic neoplasms

Haemangiomas and lymphangiomas are embryonic tumours. Lymphangiomas as well as haemangiomas of the temporal bone, especially involving the middle ear, are extremely rare [220, 221]. Symptoms of middle ear involvement may include conductive hearing loss and paralysis of the facial nerve [221].

5.8 Teratoma

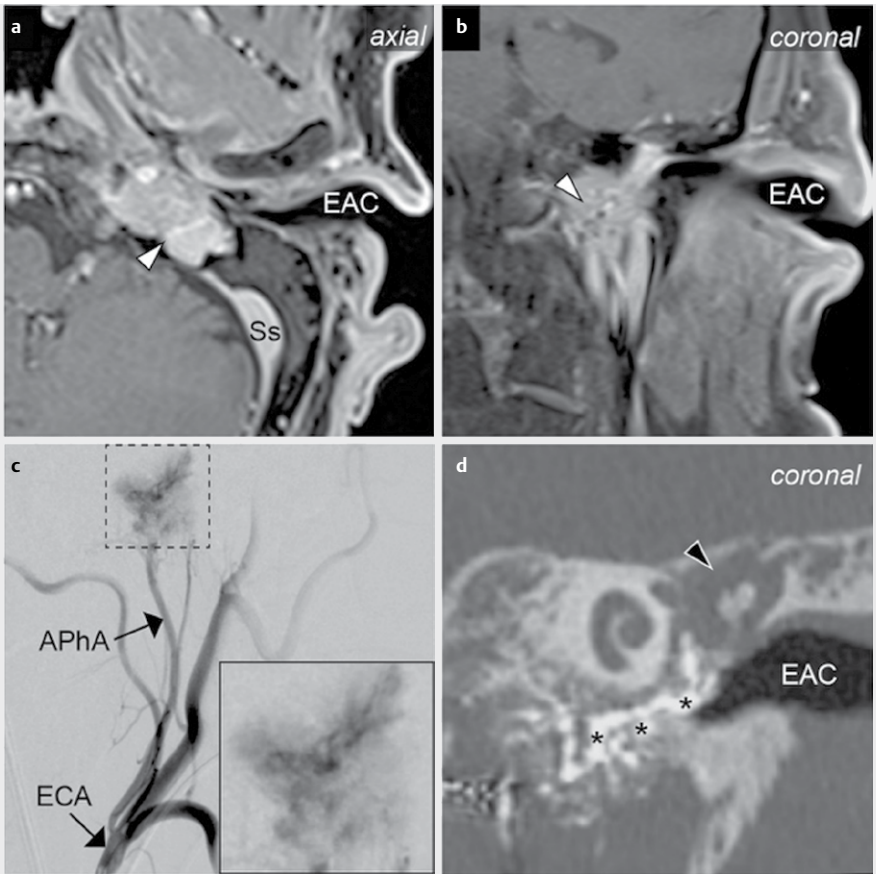
Teratoma is tissue of ectodermal, mesodermal and endodermal origin without function and clear structure with occurrence in locations not intended for it. Usually the ovaries, testes, retroperitoneum or mediastinum are affected. Occurrence at the base of the skull and rarely in the temporal bone has been described [48, 222, 223].

5.9 Tumours of the internal auditory canal, the inner ear, the cerebellopontine angle and the pyramidal tip

Tumours of the cerebellopontine angle account for around 10 % of all intracranial tumours. Nearly 90 % of all cerebellopontine angle tumours are vestibular schwannomas and meningiomas. Other cerebellopontine angle tumours include epidermoid cysts, arachnoid cysts, lipomas, schwannomas of other cranial nerves, metastases, vascular lesions (e. g. paragangliomas or haemangiomas) and cholesterol granulomas [224–226]. Cerebellopontine angle tumours cause symptoms by the compression of neurovascular structures. Typical manifestations include unilateral hearing loss, vertigo and tinnitus. Depending on the size and dignity, they may also cause facial pain, facial nerve paresis, vocal cord paralysis, dysphagia, diplopia or brainstem compression [224].

5.9.1 Vestibular schwannoma

Vestibular schwannoma is a benign tumour that originates from the nerve sheath of one of the two vestibular nerves or, in rare cases, from the cochlear nerve [227]. The nerve of origin of the vestibular schwannoma can be determined by vestibular five-receptor diagnostics, consisting of a stimulation of the three semicircular canals by using video head impulse test or caloric stimulation of the lateral semicircular canals as well as derivation of ocular and cervical vestibular evoked myogenic potentials [228]. Further, functional diagnostics include subjective (pure tone audiogram, speech audiogram) and objective (brainstem audiometry, otoacoustic emissions) audiometry. If there is an asymmetry in the pure-tone audiogram of ≥ 20 dB in two adjacent frequencies or unilateral tinnitus or an asymmetry ≥ 15 dB in two adjacent frequencies between 2 and 8 kHz, radiologic imaging by contrast MRI is recommended [229]. High-resolution radiological imaging allows an early detection even of small tumours (▶ **Fig. 12**). Vestibular schwannomas comprise 80 % of tumours in the cerebellopontine angle, making them the most common tumour entity in the posterior fossa in adults [230]. Treatment options include surgery, observation (especially of small or large stationary tumours) and radiotherapy. Treatment decisions are individualized and follow an interdisciplinary approach: In asymptomatic vestibular schwannomas, the treatment concept usually consists of regular radiological imaging following fixed intervals together with clinical controls of symptom progress ("wait and control", "wait and scan", "wait and test and scan", "watchful waiting") [231]. Growth rates of between 1 and 2 mm per year up to growth rates of 17 mm per year are reported in the literature [232, 233]. Treatment is indicated in case of growth (> 3 mm/year [234]), brainstem contact or brainstem compression, and the occurrence of disabling vertigo. Further indications for



▶ **Fig. 11** Paranglioma of the left tympanic glomus. **a**, **b** Contrast-enhanced T1-weighted MRI image with fat suppression showing the paraganglioma (white arrowhead) obliterating the tympanic cavity. **b** Contrast-enhanced T1-weighted MRI image after contrast agent administration. The vessels present as the pathognomonic hypointense "salt-and-pepper" pattern of paraganglioma with flow interruptions due to high vascularity (white arrowhead). **c** Selective angiography shows the paraganglioma as a typical "tumour blush" (dashed box, enlarged view as inset bottom right) with vascular inflow from the ascending pharyngeal artery **(APhA)** from the stromal area of the external carotid artery **(ECA)**. **d** Coronary CT of the temporal bone after successful embolization with liquid histoacryl (asterisks). **EAC:** external auditory canal; Ss: sigmoid sinus.

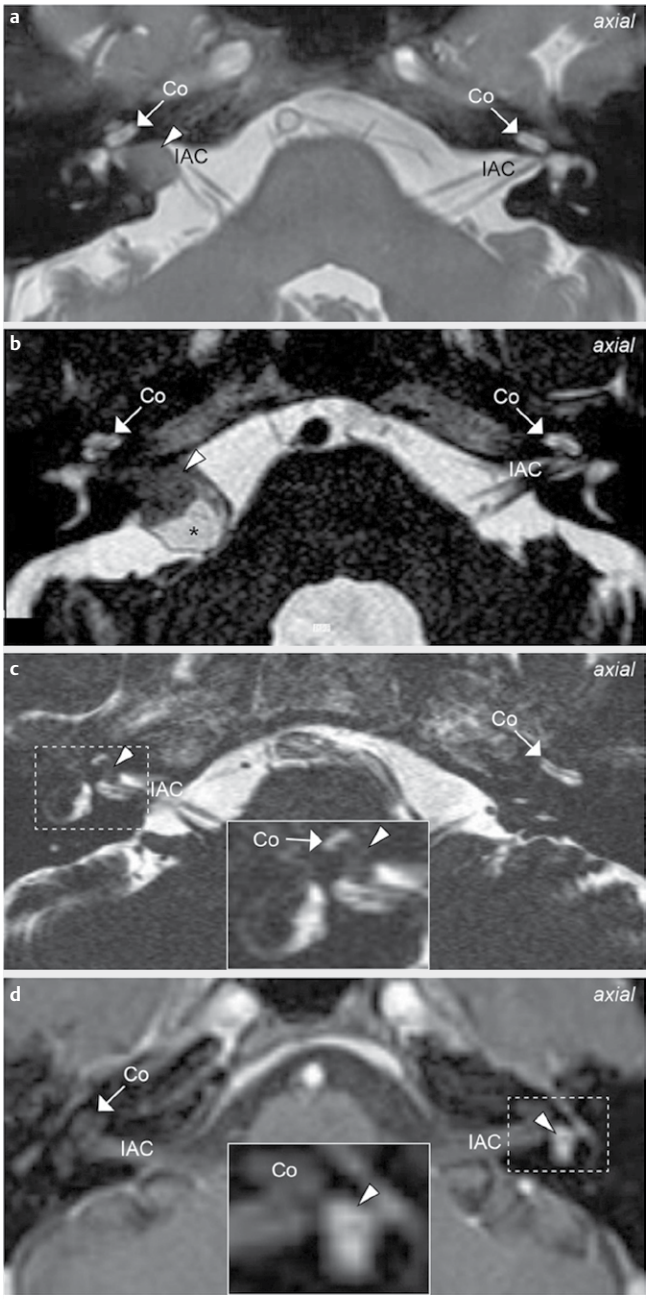
treatment are deterioration of hearing, balance or facial nerve function. The occurrence of intralabyrinthine schwannomas (intracochlear and/or intravestibular), on the other hand, is much more uncommon and is reported in only up to 10 % of vestibular schwannomas [52, 235–237]. While vestibular disorders are the most common initial symptomatology of vestibular schwannomas of the cerebellopontine angle, intralabyrinthine schwannomas are of particular importance in the differential diagnosis of sudden hearing loss [237]. In the case of transmodiolar or transmacular growths, they are particularly challenging due to the necessary trade-off between complete resection versus possible hearing rehabilitation using a cochlear implant [238].

5.9.2 Meningioma

Meningiomas usually occur in a sporadic fashion, but may also be associated with hereditary syndromes, such as neurofibromatosis type II. They make up the second most common entity of cerebellopontine angle tumours, accounting for 3 % to 10 % [239]. Most meningiomas are benign and slow growing. Only around 1 % of meningiomas in the cerebellopontine angle become symptomatic. Meningiomas differ from vestibular schwannomas in pathogenesis and radiological features [240, 241], but are hard to distinguish in terms of clinical presentation and audiovestibular examination [224, 239].

5.9.3 Epidermoid cyst

Epidermoid cysts comprise approximately 5 % of cerebellopontine angle tumours. They develop from ectodermal inclusions scattered during embryogenesis. The cyst is lined with squamous epithelium and filled with lamellae of exfoliated corneal debris. Most epidermoid cysts are benign. Squamous cell carcinomas arising from epidermoid cysts are rarely reported [242, 243]. Epidermoid cysts have a higher rate of involvement of the facial nerve and trigeminal nerve compared with vestibular schwannomas. Other leading symptoms that contribute to the differential diagnosis may include hemifacial spasm, facial hypaesthesia or neuralgia [224, 239]. In addition, a distinction can be made on the basis of radiological imaging [241].



▶ **Fig. 12** Localization of vestibular schwannoma. **a** High T2-weighted MRI image of a 56-year-old patient with intrameatal vestibular schwannoma of the right side (white arrowhead). **b** Highly T2-weighted MRI image of a 68-year-old patient with intra- and extrameatal vestibular schwannoma of the right side (white arrowhead) with cystoid portion (star) with brainstem contact. **c** Strong T2-weighted MRI image of a 49-year-old patient with intracochlear schwannoma with transmodiolar growth of the right side (white arrowhead) (dashed box, enlarged view as inset at bottom centre). **d** T1-weighted MRI image after contrast agent administration of a 49-year-old patient with intravestibular schwannoma in the left vestibule with transition to the horizontal semicircular canal (white arrowhead) (dashed box, enlarged view as bottom centre inset). **Co:** cochlea; **IAC:** internal auditory canal.

6 Infectious Diseases

6.1 Tuberculosis

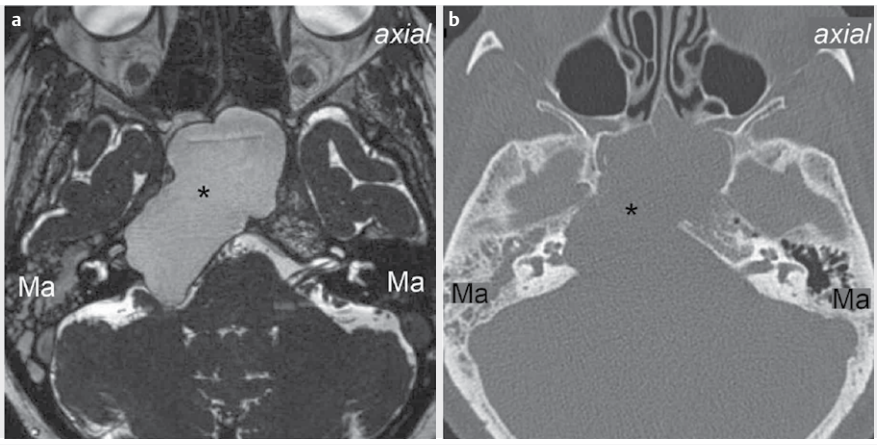
Ear manifestation of tuberculosis typically involves the occurrence of multiple tympanic membrane perforations, that may be bilateral. In up to 3 % worldwide, acute otitis media is caused by tuberculosis [244]. An association between the reactivation of tuberculosis and the HI virus is assumed [245]. The disease usually manifests with an oedematous swelling of the tympanic membrane and an infiltration by giant cells. Characteristic formations of tubercles from epithelioid cells, lymphoid cells and Langerhans cells are found. As a result, ulcerations and purulent exudates develop, followed by bone resorption. Treatment in the early stages consists of antibiotic or surgical treatment [246]. Frequently, under the clinical appearance of recurrent mastoiditis or persisting inflammation after surgery, surgical treatment is carried out and the microbiological diagnosis only follows postoperatively with retard [247]. Particularly in cases of prolonged otitis media and/or multiple tympanic membrane perforations, tuberculosis has to be considered. It is diagnosed by the microbiological detection of acid-fast bacilli from ear swabs or tissue biopsy.

6.2 Otosyphilis

Syphilis (lues) is caused by Treponema pallidum, may occur congenital or acquired and may affect the audiovestibular system as part of neurosyphilis. The incidence of hearing loss, that mostly affects the inner ear, is between 18 % and 90 % in syphilis [248]. Immunosuppressed patients with HIV infection are particularly at risk for the occurrence of otosyphillis [249]. In addition to the typical meningo-neuro-labyrinthitis, osteitis of the temporal bone may also occur. This can also affect the ossicular chain [250]. Antibiotics and steroids are used for treatment.

6.3 Necrotizing (malignant) external otitis

Otitis externa necroticans is an aggressive osteomyelitis of the temporal bone and skull base. Its origin usually is the bony part of the external auditory canal. It is most commonly caused by Pseudomonas aeruginosa, but fungal colonisation is also increasingly important and may influence treatment decisions [251, 252]. The disease typically affects older adults, with diabetes mellitus as an important risk factor [253–255]. Histology reveals a transformation of bone into granulation tissue with fusion of the mastoid and temporal bone. The disease predominantly spreads along compact bone [256, 257]. If left untreated, the disease can lead to life-threatening complications such as mastoiditis, cranial nerve palsies, phlebitis or thrombosis of the sigmoid sinus or internal jugular vein, sepsis and osteomyelitis of the skull base. Therefore, in prolonged courses of otitis externa with a softened bone of the auditory canal and in patients with diabetes mellitus, radiological CT imaging and biopsy are indicated. In addition to the topical antiseptic and antibiotic treatment, treatment consists of systemic antibiotics, that should be administered in accordance with the ear smear for at least 4–6 weeks and, if necessary, extended with antifugal medication [258]. If there is no improvement with conservative therapy, surgical treatment may be necessary [255]. Hyperbaric oxygen therapy is another alternative therapy [259].



▶ **Fig. 13** Mucocele involving the right petrous apex (asterisk) with cranial nerve involvement VII & VIII. **a** T2 weighted MRI of the mastoid. Hyperintense signalling of the mucocele that extends into the sphenoid sinus with complete obstruction of the aerated mastoid cells. **b** CT of the temporal bone. Bone destruction of the petrous bone with loss of the bony border to the cerebellum is shown. **Ma:** Mastoid.

6.4 Cholera

The vibrio-bacteria family consists of more than 200 serogroups. The most common types are the cholera toxin-producing serogroups O1 and O139, which cause epidemic cholera followed by diarrhoea [260, 261]. A second group is characterized by self-limiting milder gastrointestinal infections, which may be associated with extraintestinal infections such as sepsis, wound infection, skin and soft tissue infections, peritonitis, meningitis, cholangitis and ear infections [262, 263]. The pathogen is primarily transmitted via unfiltered or insufficiently filtered drinking water and contaminated food. A few cases of otitis media or otitis externa caused by Vibrio cholerae non-O1/O139 have been reported in the literature [263]. Bathing in swimming pools, stagnant water or the Baltic Sea is considered a risk factor [263].

In summary, inflammation of the external auditory canal and middle ear warrants microbiological examination by smear and/or tissue biopsy to detect rare pathogens, especially in cases of prolonged disease courses.

7 Varia

7.1 Pneumatocele of the temporal bone

Pneumatocele of the temporal bone is a cystic cavity that increases in size, is filled with air and may communicate with the retroauricular skin or extradural cranial spaces beyond the borders of the temporal bone. Infections or trauma are discussed to be the causes [264]. Symptoms may include headache, dizziness as well as an increase of symptoms due to Valsalva manoeuvres [265]. The diagnosis is confirmed on temporal bone CT by the presence of septations within the pneumatocele [266]. The therapy concept consists of careful evacuation and closure of the aerated mastoid cells [267].

7.2 Otogenic primary mucocele of the mastoid

Mucoceles are slow-growing cysts that result from distension of a hollow organ or cavity with mucus. Mucoceles show signs of chronic sterile infection and have the ability to cause bony remodelling or reabsorption. Mucoceles may be primary or secondary to chronic inflammation, trauma, scarring from previous surgery or radiotherapy and, less common, to neoplasia [268–270]. Their occurrence in the mastoid (▶ **Fig. 13**) is very rare, with almost exclusively case reports in the literature [271–279]. In the case of bony erosions and destruction at the mucocele margin, intra- and extracranial complications may occur [280]. Treatment of mucocele includes marsupialisation, in which it is drained via natural drainage routes while the mucosa is spared. Surgical treatment is indicated for mucocele in the mastoid, as it may extend with the risk of infection and intra- or extracranial complications [280]. Appropriate surgical treatment may include complete removal of the lesion by mastoidectomy to reduce the risk of recurrence [280].

7.3 Otogenic pneumocephalus

Otogenic pneumocephalus is characterized by air penetrating intracranially through a dural defect into the subarachnoid space, brain parenchyma or ventricular spaces. Symptoms include headache, otorrhoea, meningism and dizziness [281]. Possible causes described in the literature are trauma, complications of ear surgery, otitis media or cholesteatoma [282]. If caused by trauma, otogenic pneumocephalus may be accompanied by a cerebrospinal fluid fistula. If caused by otitis media or a cholesteatoma, the complication of an intracranial abscess may occur. Therapy consists of the combination of pressure relief and defect closure. In postoperative tension pneumocephalus, immediate needle aspiration should be performed. In persistent pneumocephalus, surgical revision closing the defect is indicated [282].

7.4 Spontaneous (meningo)encephalocele

A thinned tegmen tympani is considered a risk factor for the development of spontaneous encephalocele, which may be associated with CSF leaks. The possible mechanisms for thinning or erosion of the tegmen tympani include congenital defects, chronic middle ear disease, intracranial hypertension, trauma and obesity [283–285]. The symptomatology of spontaneous encephaloceles may consist of conductive hearing loss, vertigo, oto-liquorrrhoea or aural fullness [285–287]. The diagnosis is confirmed by the combination of CT and MRI and, if necessary, additionally by the detec-

tion of β2-transferrin or β-trace protein [20]. Clinical examination may reveal a tympanic effusion. A treatment indication exists in particular in cases of CSF leak. Therapy consists of surgical closure of the defect with reinforcement of the dura and tegmen tympani. Depending on the size of the defect a transmastoid approach to the middle cranial fossa, a transtemporal approach (middle cranial fossa approach) or a combined approach may be performed [286, 287].

7.5 Ectopic brain tissue

Another rare differential diagnosis for soft tissue in the middle ear is the presence of ectopic brain tissue. Individual case reports mention manifestations in the nose, tongue, orbit [288–290] or the mastoid [291–294]. Histopathology shows evidence of brain tissue. Ectopic brain tissue may be distinguished from an encephalocele radiologically or clinically, and intraoperatively by an intact dura [294–296].

7.6 Idiopathic or spontaneous hematotympanum

The origin of idiopathic or spontaneous hematotympanum is not completely understood. It is considered to be a variant of acute otitis media [297]. Clinically, it presents with a blackish-blue tympanic membrane. The coloration of the haemolyzed blood results from recurrent bleeding in the middle ear, combined with a drainage disturbance via the Eustachian tube [297]. The bleeding is thought to originate from cholesterol granulomas, that may be a consequence of otitis media [48]. Surgical removal of the granulomas with tympanic drainage is described to be an effective therapy [298, 299].

7.7 Gorham-Stout syndrome

Gorham-Stout syndrome is a spontaneously occurring osteolysis. It is based on local proliferation of small blood and lymph vessels with subsequent progressive destruction and resorption of the bone. The symptoms depend on the manifestation site. The most common symptom is local pain. If the temporal bone is affected, deafness may occur [300]. The diagnosis is made on clinical, radiological and histological findings and by excluding the potential differential diagnoses [300, 301]. Treatment options include radiotherapy, bisphosphonates and interferon-α2b [302]. Surgical intervention may be required due to CSF leaks or medullary compression [303].

7.8 Cholesterol granuloma

Cholesterol granuloma is an inflammatory reaction to blood degradation products and presents as a cyst with a thick fibrous lining filled with brownish-yellow fluid. It can occur in the middle ear, mastoid and petrous apex and is considered to be the most common benign lesion of the petrous apex [304]. Occurrence in the mastoid and middle ear is reported to be much less common [304]. Poor pneumatization or haemorrhage in the mastoid are considered to be the predisposing factors [305]. Cholesterol granulomas in the middle ear and lateral skull base are often asymptomatic, but may lead to cephalgia, hearing loss or, with increasing size, to cranial nerve deficits [306]. MRI shows high signal intensity in T1 and T2 sequences. CT offers information about the displacement of bony structures or bony destruction [304]. Therapy consists of either regular follow-up or surgical resection in symptomatic cases [307–309].

7.9 Giant cell granuloma

Giant cell granuloma is a reactive process triggered by trauma or inflammation [310, 311]. It is a rare bony lesion of the head and neck that manifests predominantly in the maxilla and mandible. The description of a manifestation in the mastoid is rare and consists exclusively of case reports [312, 313]. Symptomatology depends on the structures involved and may include conductive hearing loss, tinnitus, vertigo, local swelling or weakness of the facial nerve [314]. Treatment options include curettage, surgical excision and radiotherapy [315, 316]. Complete surgical resection is mandatory due to high recurrence rates followed after incomplete resection [317].

8 CONCLUSION

Rare diseases of the middle ear and lateral skull base may resemble common otolaryngologic diseases, which harbours the risk of delayed diagnosis or misdiagnois. In a case of otitis media that does not respond to antibiotic treatment, aural smear, especially for mycobacteria, needs to be performed to exclude rare infections [318]. In case of pulmonary involvement and simultaneous otorrhoea or multiple perforations of the tympanic membrane, an ear manifestation of tuberculosis should be considered. The concomitant diseases of the patient can be indicative. Especially in immunosuppressed patients with HIV infection, rare bacterial infections such as otosyphillis may occur. Furthermore, the risk of necrotizing (malignant) external otitis in elderly patients with diabetes mellitus has to be considered. In cases of protracted, recurrent or bilateral otitis, autoimmune disorders such as granulomatosis with polyangiitis may be the underlying condition.
In cases of middle ear and mastoid diseases without a response to antibiotics, a biopsy is obligatory to exclude malignancies or diseases of the haematopoietic system as well as autoimmune disorders. It is supplemented by appropriate serologic investigations. Systemic causes such as histiocytosis or vasculitis should be considered, especially in cases of bilateral destructive ear disease detected in CT-imaging associated with increased erythrocyte sedimentation rate and without other indications of infection, or in cases of long-term granulation tissue after tympanomastoid surgery with persistent otorrhoea and skin lesions.
Asymmetric hearing or balance disorders as well as deficits of the caudal cranial nerves may indicate neurological disease patterns or be the initial manifestation of neoplasms and lesions of the temporal bone. A unilateral tinnitus occurs as the first symptom in 1 to 5 % of cases in vestibular schwannoma and a pulse-synchronous tinnitus may indicate a paraganglioma or a vascular anomaly. Therefore, these symptoms should be investigated by radiologic imaging even in the absence of conspicuous tympanic membrane findings.

In the case of petrous bone lesions, the differential diagnosis includes metastasis and rare bone or cartilage tumours. For this reason, the imaging of choice usually consists of a high-resolution CT of the temporal bone. For further diagnosis, an MRI may be added. One exception is vestibular schwannoma, where the initial imaging should consist of contrast MRI. A biopsy can be performed via various access routes and confirms the diagnosis [319]. Close interdisciplinary cooperation and specific questions with information on the clinical symptoms need to be communicated with the examining histopathologists, human geneticists or molecular pathologists.

A detailed diagnosis is necessary prior to any surgical intervention. In particular if there are indications of malformations, radiological imaging is mandatory to identify anatomical variants of the temporal bone and to avoid surgical complications such as haemorrhages, CSF fistulas or injuries to the facial nerve.

For quality control in patient care and in surgical interventions, knowledge of rare diseases is an essential component and must be available to assess complicated protracted disease courses. In addition to making physicians aware of rare differential diagnoses, recording of patient data in designated registers may be helpful. Making use of cumulative data storage, the conduction of studies that go beyond case reports is enabled and further information about the individual diseases may be gained. As a consequence, an improvement of treatment options can be achieved [320–322]. Only a careful collecting and documentation of all necessary diagnostic criteria such as anamnesis, clinical findings, imaging, laboratory and results of microbiological, histological and, with increasing importance, molecular pathological and genetic examinations enable a reliable diagnosis and an adequate treatment.

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Conflict of interest

The authors declare that they have no conflict of interest.

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