OXFORD FRCPath Course: Head and Neck Pathology.

Case 1 (HI 09-17464).

Clinical History.
Male 64 years. He had previously smoked heavily for 30 years, giving up in 1992. 2009 July: larynx biopsy and laser ablation. Examination shows an irregular lesion anterior larynx, involving both vocal cords and the anterior commissure. First biopsies in June 2009 were inconclusive; in situ carcinoma, but no definite invasion.

Microscopic Findings
Fragments of atypical squamous epithelium with foci of genuine invasion. Elsewhere, in situ changes are seen. Special stains and immunohistochemistry are not needed.

Diagnosis.
Larynx – moderately differentiated squamous cell carcinoma of usual type.

Further Clinical Information.
2009 July: larynx biopsy and laser ablation. 2009 August - clinical evaluation is that the tumour is stage 1b. He was treated with radical radiotherapy. 2009 December – voice almost normal. Microlaryngoscopy shows no tumour.

Discussion.
Squamous cell carcinoma of the upper aero-digestive tract is the commonest non-skin malignancy of the head and neck[1,2]. Tobacco and alcohol are the main aetiological agents, although some tonsillar cancers are thought to be HPV-related. A further subset of oral squamous carcinomas in young people, especially women, appears to have a different molecular basis and is at present unexplained.

Several histological variants are known. Although relatively rare, they may have a higher incidence in slide seminars and exams!

Variants of squamous carcinoma of the upper aero-digestive tract:
Usual (keratinising).
Verrucous.
Basaloid.
Papillary (exophytic).
Spindle.
Acantholytic.
Adenosquamous.
Lymphoepithelial.
?HPV-associated basaloid carcinoma of tonsil.

Pre-neoplastic changes, particularly in the larynx.
Several schemes have been proposed, but none has been universally accepted[3]. There are good reasons why it is not appropriate to use a system exactly like the uterine cervix, for example,
few laryngeal carcinomas are HPV-related and there is no laryngeal equivalent of treatment by LLETZ or cone biopsy¹. This is a complex subject causing considerable problems in practice.

References


Case 2 (HI 99-17112).

Clinical History.
Male born 1935.
Childhood tonsillectomy.
Smoked 15/day from 1953-1998.
1984 Chronic rhinitis.
1991 Hiatus hernia and oesophagitis.
1999, Oct hoarseness,
      feeling of “something dangling in the throat”;
      R lower neck lump.
CT Massive exophytic tumour at level of the cricopharynx.
Biopsy (HI99-17112).

Microscopic Findings
Haematoxylin and Eosin.
The specimen consists of multiple tissue fragments. They are composed of spindle cells
arranged haphazardly, in fascicles (sometimes in a storiform pattern) and more loosely, where the
appearance resembles granulation tissue. The cellularity varies from densely packed cells to a
more loose arrangement. The spindle cells themselves vary from thin to plump. There is a
moderate to marked degree of nuclear pleomorphism. Mitotic figures are plentiful. There are
occasional scattered multinucleated giant cells and rare tiny foci of probable epithelium.

Special Stains and Immunohistochemistry.
Broad spectrum Dako-keratin (cytokeratin subtypes 1, 5, 6, 8, 13, 16) - c.80% spindle cells
stain strongly. MNF116 (cytokeratin subtypes 5, 6, 8, 17, 19) – c.50% spindle cells stain strongly.
CAM 5.2 (cytokeratin subtypes 8, 18) - c.40% cells show some reaction. CK5/6 patchy staining of
possible epithelium. EMA – only very occasional positive cells. p63 - c.30% cells positive.
Vimentin - all cell positive. ASMA, CD34 stain non-neoplastic structures only. S-100, Desmin
negative. MIB1 (Ki-67) index- c.25%.

Diagnosis.
Pharynx – spindle cell carcinoma.

Further Histopathological Findings.
In December 1999 the patient underwent a laryngectomy and this showed a polypoid
tumour in the hypopharynx, but neoplastic cells did not involve the pedicle. At the base of the
polyp there was obvious in situ and invasive poorly differentiated keratinising squamous carcinoma.
In this specimen, ASMA stained some of the tumour cells. In the neck dissection one positive
node, 75 mm long was found in levels III and IV. 14 other nodes were not involved, and the
tumour was staged as pT3, pN3.

Further Clinical Information.
In the next few months he received a course of radiotherapy and was well in January 2002.
However, two months later he was found to have a Dukes B carcinoma of the sigmoid colon (pT4,
pN0) for which he was treated with chemotherapy. In October 2003, chronic myeloid leukaemia
was diagnosed, and he received Imatinib (Glivec). No tumour was found at his most recent assessment at the head and neck clinic in August 2007. His CML was under control in October 2007.

Discussion.

Spindle cell carcinoma (SpCC) of the upper aero-digestive tract is a rare malignancy that affects elderly male cigarette smokers as a polypoid tumour\(^1\). In the larynx, it accounts for 1.3% of all squamous carcinomas. The clinical behaviour is generally analogous to conventional squamous cell carcinoma\(^2\). The commonest sites are (in descending order of frequency): the larynx (true cords more often than false cords or supraglottis), the oral cavity (lips, tongue, gingival, floor, buccal mucosa), skin, tonsils and pharynx\(^3\). Histologically, most SpCCs show both squamous and spindle cell populations; the former is typically characterised by a relatively minor focus of invasive or in situ carcinoma and the latter by a predominantly pleomorphic sarcoma-like pattern resembling a fibrosarcoma or so-called malignant fibrous histiocytoma. The growth pattern varies and includes fascicular, storiform, or palisading, sometimes with a myxoid stroma. Occasionally, there are paucicellular tumours with dense collagen and only a few atypical spindle cells, often concentrated around blood vessels. Heterologous elements such as bone or cartilage can be present, and may even be malignant. Immunostaining of paraffin sections detects positivity for keratin in the spindle cell population in c.65% of tumours. In Lewis’ series, the most sensitive markers were 34βE12 and AE1/AE3. More recent studies show that other markers help in identification, including EMA and p63\(^4,5\). Identical immunohistochemical p53 expression patterns in the epithelial and spindle cell components support the concept that these phenotypically divergent cell populations share similar developmental pathways. The spindle cell component is non-diploid in most tumours and frequently has a DNA profile similar to that of the co-existing squamous element. The combined presence of keratin positivity and non-diploid DNA content in the spindle cell population supports the sarcomatoid carcinoma theory of histogenesis.

The differential diagnosis includes nodular fasciitis (little or no atypia), true fibrosarcoma or leiomyosarcoma (extremely rare at mucosal surfaces), inflammatory myofibroblastic tumour (no epithelial elements or atypical mitotic figures, ALK-1 positivity) and especially a granulation tissue polyp.

The treatment for SpCC is similar to that for conventional squamous carcinoma. The prognosis varies: polypoid glottic tumours appear to have the most favourable outcome with a 90% three year survival, whereas supraglottic, hypopharyngeal, sinonasal and oral SpCCs did poorly regardless of their gross appearance. Batsakis et al concluded that SpCCs exhibit a more aggressive biological behaviour than most conventional squamous carcinomas\(^6\).

References.

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Case 3 (HI 00-23266).

Clinical History.
Male 54 years. This former quarry worker smoked 25 cigarettes per day. Apart from appendicitis in 1959 he had been well, until November 2000, when he complained of a right sided sore throat for 3½ years, and he had noticed that his voice had changed over the most recent 3 months. The following month a laryngoscopy showed an extensive exophytic tumour filling the right piriform fossa, as well as a separate tumour on the left. There was a vocal cord palsy. Biopsies of both lesions were performed. It was also noted that an uncle had died of throat cancer.

Microscopic Findings.
Haematoxylin and Eosin.
The tissue from the right piriform fossa shows several fragments comprising mainly tumour, which invades the little remaining fibrous tissue. There is plentiful necrosis. The overall appearance of the tumour is that of basaloid islands of densely-packed nuclei with some peripheral palisading. Plentiful mitotic figures are seen. There are small quantities of myxoid stroma. The overlying squamous epithelium is atypical in places, partly reflecting a repair process, but there is also probable genuine dysplasia.
The tumour in the left piriform fossa is an in situ and invasive poorly differentiated squamous carcinoma of usual type with rare foci of keratinization.

Special Stains.
No (PASD+) epithelial mucin, but stromal myxoid areas stain with alcian blue.

Immunohistochemistry.
Cytokeratins: LP34 (cytokeratin subtypes 5, 6, 18) +++; CAM5.2+, CK7 and 20 both negative. EMA – focally+. Neuron specific enolase (NSE) – cross reaction, probably negative. Chromogranin A and synaptophysin were both negative. Calponin - cross reaction. S-100, ASMA, SMMHC all negative.

Diagnosis.
Pharynx - basaloid squamous cell carcinoma.

Further Histopathological Findings.
In December 2000 a laryngectomy was performed with a neck dissection. The right piriform fossa contains a lobulated and ulcerated tumour $60 \times 35$ mm. Excision is complete, but only just as it is 1 mm from the nearest mucosal edge. The tumour is seen to be in continuity with the lesion in the left piriform fossa. It is a basaloid squamous carcinoma similar to that seen in the biopsy, and small areas of conventional squamous carcinoma are noted, not just on the left. The radical neck dissection revealed 47 benign lymph nodes.

Further Clinical Information.
**Discussion.**

Basaloid squamous cell carcinoma is a high grade variant of squamous carcinoma with a predilection for the tongue base, supraglottic larynx, hypopharynx (piriform fossa) and the palatine tonsil. It is characterized histologically by an invasive neoplasm composed of basaloid cells intimately associated with a dysplastic squamous epithelium, in situ or frankly invasive squamous cell carcinoma of usual type. It occurs more commonly in men in the 6th and 7th decades of life. Aetiological factors include excessive alcohol and/or tobacco use\(^1,2,3\).

Grossly these tumours are described as firm to hard tan-white masses, often partly necrotic, up to 60 mm in diameter. Histologically, basaloid squamous cell carcinoma is an invasive neoplasm composed of basaloid cells with an associated squamous component, and demonstrating a variety of growth patterns, including solid, lobular, cribriform, cords, trabeculae and gland-like or cystic growth. The basaloid component consists of cells with pleomorphic, hyperchromatic nuclei, scanty cytoplasm and increased mitotic activity. Peripheral nuclear palisading may be present, and comedo-like necrosis may be seen in the centres of the lobules. The squamous element (usually a minor component) includes dysplastic squamous epithelium, foci of abrupt keratinisation, in situ or invasive squamous carcinoma. Continuity of either element with the surface may be seen.

Immunoreactivity is consistently present to epithelial markers, such as cytokeratins (most are CK7\(^+\)), EMA and even CEA. p63 is also always positive, and has a different staining pattern to adenoid cystic carcinoma\(^4\). Neuroendocrine markers are usually negative. Variable expression can be seen with S-100, actin and vimentin.

The treatment of choice includes radical surgical excision with radio- or chemotherapy. Basaloid squamous cell carcinoma is an aggressive, high grade tumour with a tendency to be multifocal, deeply invasive and metastatic at an early stage. Metastases occur via lymphatics and blood vessels, and include both basaloid and squamous components. The tumour has a high mortality rate, especially in comparison to squamous carcinoma of usual type. This may be due to an innately greater degree of aggressiveness, but it has also been suggested that the poor outcome is a factor of the site of origin, and that basaloid carcinoma is frequent at sites (e.g. base of the tongue) where squamous carcinoma of usual type also has a similarly poor prognosis stage for stage.

**References.**


Case 4 (HI 09-10340).

Clinical History.
Born 1919
1993 lump L tongue. Getting bigger. Painless. Papillomatous lesion 6mm. surrounded by 10 mm halo of leukoplakia.
2009 March lump on L tongue. 40 mm area of leukoplakia. 15 mm diameter verrucous lesion.
2009 May Left partial glossectomy for mass on tongue with the clinical appearance of a verrucous carcinoma.
Macroscopically, there is a warty white nodule 15 × 10 × 6 mm.

Microscopic Findings.
Exophytic papillomatous squamous proliferative lesion with deep parakeratotic clefts and “church spire” like structures. The lesion extends into the underlying tissue in the form of broad-based squamous club-shaped papillae – so-called “elephant feet”. There is only a little atypia at the edges of the clubs with a few mitotic figures in the basal layer, none of which is abnormal. There is no component of usual type squamous carcinoma.

Diagnosis.
Tongue – verrucous carcinoma.

Further Clinical Information.
No lymphadenopathy.
2009 May, tumour removed.
No adjuvant therapy.
2009 December well, with no lymphadenopathy.

Discussion.
Although uncommon, 75% of all cases of verrucous carcinoma occur in the oral cavity. It is exophytic, warty, slowly growing variant of squamous carcinoma with pushing margins. It typically affects older males. HPV types 16 and 18 have been identified in 40% of cases. Surface ulceration and haemorrhage are not seen, except when there is an additional component of squamous carcinoma of usual type.
VC invades the underlying tissue with a pushing, rather than infiltrating border. A dense lympho-plasmacytic infiltrate is common, but not seen in every case.
The surrounding epithelium shows progressive transformation from hyperplasia to VC. With extensive surgical removal, and without neck dissection, the 5 year survival rate is 80-90%, although 8% of patients require further surgery during that time.
No molecular or other markers have been shown to have prognostic significance for oral VC. However, about 20% of cases contain a component of squamous carcinoma of usual type, and such tumours have a greater tendency to recur and metastasise to lymph nodes. Hence all VCs must be fully sampled.

References.

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Case 5 (HI 09-11096).

**Clinical History.**
Male 41 years. IV drug-user for 20 years. Smoked tobacco, but did not drink alcohol. HIV and HBV negative, but HCV positive.

In April 2009, he presented with an enlarged lymph node in the left side of the neck at level II. FNA showed poorly-differentiated carcinoma. No evidence of a primary on clinical examination or at endoscopy, so biopsies were taken from the nasopharynx, base of the tongue and the left tonsil. This biopsy is from the tonsil.

**Microscopic Findings.**
The tonsil shows extensive poorly differentiated non-keratinising squamous carcinoma, which is in situ as well as invasive. The tumour is strongly positive for p16.

**Diagnosis.**
Tonsil – non-keratinising squamous carcinoma, probably HPV-associated.

**Further Clinical Information.**
2009 June - liver biopsy showed metastatic carcinoma.
Treated with chemotherapy.
2010 January – alive with disease.

**Discussion.**
HPV-associated squamous carcinoma of the oropharynx has recently been recognised as a special subtype of head and neck squamous carcinoma.

Overall, rates of head and neck squamous carcinoma in the USA have been dropping over the past 30 years, as rates of smoking have decreased. However, rates of oropharyngeal carcinoma have been rising during this period, particularly in men of a younger age (40-60 years) who have never smoked tobacco. This is thought to be due to oral sex and perhaps use of marijuana.

Pathologically, they arise from the tonsillar crypts, and have a lobular growth. Many are infiltrated by lymphocytes. They lack keratinisation and often have a basaloid morphology.

The best way to identify these tumours is with ISH for HPV 16, but p16 immunohistochemistry is a fair substitute, although perhaps as many as 30% are false positive.

The outcome is much more favourable than in usual type squamous cell carcinoma.
Clinical History.
Female 22 years. Beta thalassaemia trait.
Spent most of the previous year in India during her pregnancy.
Third trimester began to feel nauseous. Anaemia 8.4.
12 days post partum. Presented with a 2 month history of sore throat and vomiting.
The clinical diagnosis was oesophageal reflux and laryngitis.
One month later she complained of increasing weight loss, lassitude and sore throat.
A biopsy of the epiglottis was performed.

Main microscopic findings.
Epiglottis mucosa with a heavy chronic inflammatory infiltrate including non-necrotising giant cell granulomas. No organisms are identified with ZN or PAS.

Diagnosis.
Larynx-tuberculosis.

Further Clinical Information.
Chest XR showed a military infiltrate, suggestive of tuberculosis. Positive cultures were identified in sputum and bronchial washings. Chemosensitive antibiotic therapy was started.
2007 Responded well.
2008 July well. No evidence of recurrent disease.

Discussion.
Granulomatous inflammation can be seen in sarcoidosis as well as rare fungal infections. Foreign body type granulomas may be seen after Teflon injections or in amyloidosis.
Case 7 (Tawam 99-01444).

**History.**
Female 25 years old. She presented with a 3 month history of anosmia. Examination revealed an ill-defined mass lesion in the nasal cavity and both ethmoids, and this extends to involve the cribriform plate and the anterior cranial fossa.

**Microscopic Findings.**

*Haematoxylin and Eosin.*
The sections show fragments of bone, sinonasal mucosa and soft tissue. There are areas of dense fibrosis and an inflammatory infiltrate of lymphocytes, plasma cells, macrophages with some eosinophils and neutrophils. There are scattered prominent multinucleate giant cells, and a few discrete granulomas are noted.

*Special Stains.*
Fungal hyphae are identified with PASD and Grocott’s methanamine silver methods.

**Diagnosis.**
Nose – Invasive fungal sinusitis, possibly Aspergillus.

**Further Clinical Information.**
No follow-up information is available.

**Discussion.**
Sinonasal fungal disease can be divided into four groups:\(^1\,\^2\,\^3\):

a). Non-invasive colonization of paranasal sinuses (“fungus ball”).
b). Non-invasive hypersensitivity reaction to fungi (allergic fungal sinusitis).
c). Invasive indolent sinusitis.
d). Invasive fulminant fungal rhinosinusitis.

Patients with non-invasive colonization typically have chronic sinusitis, and only a few will suffer facial pain or sense of fullness. Imaging often shows a single opacified sinus. Almost all cases are due to Aspergillus sp. Treatment is debridement, and there is no role for antifungal drugs.

Allergic fungal sinusitis is a non-invasive fungal pansinusitis that occurs in immunocompetent individuals with a history of atopy and peripheral eosinophilia. Although Aspergillus can cause this in a similar way to bronchopulmonary aspergillosis, most sinonasal cases are due to other fungi. Microscopy shows abundant laminated mucin containing cell debris and inflammatory cells, particularly eosinophils with Charcot-Leyden crystals. Fungal hyphae are present, but there is no invasion of bone or mucosa.

Chronic invasive fungal sinusitis (invasive indolent sinusitis) patients are usually immunocompetent and have a protracted clinical course.

Invasive fulminant fungal rhinosinusitis is a medical emergency. Patients are usually immunocompromised secondary to poorly controlled diabetes mellitus, post-transplantation, HIV infection, malignancy and/or chemotherapy or corticosteroid therapy. There are typically
thrombosed blood vessels due to the tendency of the fungi to invade blood vessel walls, tissue necrosis and acute inflammation, although in some cases there is little inflammatory reaction. Many fungi can be involved, but the most frequent are Aspergillus species, and non-hyphal organisms such as cryptococcus may occur. Mucormycosis (phycomycosis) is usually seen in poorly controlled diabetics, although it can occur in non-immunocompromised hosts. The most often involved sinus is the maxillary antrum, followed by the ethmoid, sphenoid and frontal paranasal sinuses. Fulminant infection may spread to the cranial cavity by direct extension, vascular emboli, perineural invasion or through the cribriform plate. The mortality rate for this form is 25% and is higher if there is a predisposing systemic disease, such as diabetes. Treatment should be aggressive with surgical debridement and systemic antifungal drugs.

Other infections.

Rhinosporidiosis.

This disease is endemic in India, but also found elsewhere including South America, Africa and rural parts of the USA. It is associated with stagnant pools of water, dust and trauma, and there is animal to human transmission. It is characterised by hyperplastic polyps in the nasal cavity with a chronic lymphoplasmacytic infiltrate. Microscopically, there are numerous globular cysts up to 200 µm in diameter, each containing multiple spores. The organism is not a typical fungus, and is now thought to be a blue-green alga.

Rhinoscleroma.

This disease is endemic to Africa, parts of Latin America, Egypt, north and central Africa and east/central Europe (particularly Ukraine and Belarus). It is associated with crowded dwelling and poor sanitary conditions, and the cause is Klebsiella rhinoscleromatis, a Gram negative coccobacillus. The disease starts in the nasal septum, later involving the nasopharynx. It may cause nasal obstruction in up to 94% of cases, nasal deformity, upper lip swelling or ulceration of the palate. Histologically, there are three stages (exudative, proliferative and fibrotic). In the exudative phase, there is a dense lymphoplasmacytic infiltrate, together with oedema, suppurative necrosis and squamous metaplasia of the overlying epithelium. In the proliferative phase, there are numerous foamy macrophages containing bacilli (Mikulicz’s cells). In the fibrotic phase, there is scarring and chronic inflammation, but Mikulicz’s cells are rare to absent. The organisms are best demonstrated by Giemsa or Warthin-Starry stains, and cultures have only a 50% yield. A diminished T-cell response explains the chronicity, and cases have been reported in AIDS. Treatment is surgical ablation and antibiotics, such as Tetracycline or rifampicin.

References.


Case 8. (HI 85-02636).

**Clinical History.**
Male born 1910. He had previously been well, until February 1985 when he presented with a 2 month history of loss of balance, 3 weeks of cough and one week of chest pain. He had also developed deafness of the left ear on the day before admission. ESR 97, Hb 13.5, peripheral blood white cell count (WCC) 15.8. ANCA was not available at the time. A chest X-ray showed shadowing of the right mid zone. There was no response to antibiotics, and a week after admission, investigations showed ESR 120, White cell count 15.8, creatinine 112. A lung biopsy was performed. He was ventilated, but began to improve and two weeks later, his ESR 31, WCC 18.9, creatinine 97. He developed microscopic haematuria and a renal biopsy was performed. By the end of March he was able to go home, but was readmitted to hospital on 10.IV.1985 with a one day history of discolouration of the nose and swelling of the face. His ESR was 106 and creatinine 564. A nasal biopsy was performed.

**Microscopic Findings.**

*Haematoxylin and Eosin.*
Tiny fragments of sinonasal mucosa with a heavy mixed inflammatory infiltrate comprising neutrophils, lymphocytes, plasma cells, macrophages, occasional eosinophils. Some fibrin deposition, possibly in small blood vessel walls. The surface epithelium shows reactive atypia, and there is some exudate on the surface. This biopsy by itself is non-diagnostic, and should be considered as heavy non-specific mixed inflammation.

*Special Stains.*
MSB highlights fibrin in the exudates and, possibly also in a vessel wall. PASD - no fungi.

**Further Histopathological Findings.**
A lung biopsy showed numerous microscopic foci of necrosis apparently centred on alveolar walls, and these were surrounded by numerous neutrophils and macrophages. No true granulomas or overt vasculitis were seen. There were no inclusion bodies and special stains for organisms were negative. The alveolar spaces contained a fibrin-rich exudate with desquamation of type 2 pneumocytes. In the renal biopsy immunofluorescence was negative; 3/16 glomeruli showed a focal segmental necrotizing glomerulonephritis, involving the afferent arteriole in one. Tubules contained red cell casts. Small to medium sized blood vessels showed no abnormality. An oesophageal biopsy showed ulcerated inflamed mucosa with fibrinoid necrosis of a submucosal blood vessel, i.e. vasculitis. Even though no granulomas were seen, the appearances were consistent with Wegener’s disease.

**Diagnosis.**
Nose - Wegener’s disease.

**Further Clinical Information.**
Nasal biopsy in April 1985. Treatment was begun with Predisolone, Azathiaprin and Cyclophosphamide. Four days later he developed haemorrhagic oesophagitis. A week later he had improved with an ESR of 42 and a creatinine of 277. At the beginning of May he again relapsed and died four weeks afterwards.
Discussion.

Wegener’s granulomatosis is a chronic systemic disease of unknown aetiology\(^1\). It is characterized by a granulomatous vasculitis of the upper and lower respiratory tracts together with glomerulonephritis\(^2\). In addition, variable degrees of disseminated vasculitis involving small arteries and veins may occur. The mean age of onset is about 40 years and the sex incidence is roughly equal. ENT involvement occurs in 92% of patients during the course of their disease, and other sites affected include the kidneys (77%), lungs (85%), skin (46%) and joints (67%)\(^3\). Involvement of the ENT areas includes sinusitis, nasal disease (obstruction and rhinorrhea and eventually cartilage and bone destruction), otitis media, hearing loss, and less frequently subglottic stenosis, ear pain or oral lesions. The most important clinical test is cANCA (anti-neutrophil cytoplasmic antibody), but this is not specific or sensitive enough to identify every case.

Histologically, Wegener’s granulomatosis shows a variety of changes mainly in two patterns: these are destructive necrosis with inflammation and fibrinoid change, and acute necrotizing vasculitis involving all types of vessels, later evolving to scarring. The inflammation is partly granulomatous with necrosis, and there is often an acute and chronic inflammatory infiltrate including giant cells and eosinophils. None of these changes is really specific, and the diagnosis is made taking into account the clinical features, as well as the serology and histopathological findings. An important practical point is that any sinonasal biopsy must be deep enough, as the overlying crust will just show necrosis, granulation tissue and non-specific acute on chronic inflammation\(^4\).

The mean survival without treatment is only 5 months. The recommended therapy is cyclophosphamide and steroids, and 75% of patients will achieve complete remission\(^3\).

References.


Other reference:

**Clinical History.**

Male 61. Proptosis of left eye for 6 weeks, with blocked left nostril and discharge. Also numbness of left side of the face. MRI and endoscopy show an irregular haemorrhagic mass filling the whole left nasal cavity.

**Microscopic findings.**

Tissue fragments, partly lined by nasal epithelium infiltrated by a population of lymphoid blasts. Small foci of necrosis are noted.

**Immunohistochemistry.**

CD3 +, CD3 + (cytoplasmic), CD7 +, TIA-1 +, CD56 + (variable), EBER +.

Negative: CD4, CD5, CD8, CD10, CD20.

**Diagnosis.**

Nose - NK/T-cell lymphoma.

**Further Clinical Information.**

Recent case.

**Discussion.**

Previously known by a variety of names, such as lethal midline granuloma/reticulosis and angiocentric lymphoma, the present terminology is NK/T-cell lymphoma. It is most common in Asia, Africa and Latin America, but cases do occur in Europeans, as here. There is a strong association with EBV infection.

It is commoner in men with a wide age range at presentation (13-80). Approximately 50-60% of patients have localised disease at presentation, although this may include bone and nasal septum destruction. 25% have involvement of lymph nodes, bone marrow or other sites.

There is a broad morphological spectrum of lymphoid cells, admixed with plasma cells, histiocytes, eosinophils and neutrophils. The atypical cells vary in number and size, and often show invasion or clustering around blood vessels. Necrosis is usual and may be extensive, and several biopsies may be needed to identify the neoplastic cells. The cells are usually positive for CD56, but less frequently with CD57, CD16. They are also positive with CD2, CD45RO, CD3 and CD43.

The differential diagnosis includes destructive lesions of the nasal septum such as infections (especially fungi), Wegener’s disease, cocaine abuse and other lymphomas.

Patients with localised disease often respond well to radiotherapy or chemotherapy.
Case 10 (HI 09-04317).

Clinical History.
Female 87 years.
1989 Nasal polypectomy.
2008 December Nasal blockage gradually worsening over past 10 years.
On Examination: marked posterior polyps filling the left nasal cavity.
2009 February, at operation - Unilateral polyp in left nose and sphenoid sinus, arising posteriorly.

Microscopic findings.
Endophytic growth of hyperplastic ribbons of basement membrane enclosed multi-layered epithelium, 5-30 cells thick. There is no significant atypia, but a few basal mitoses are seen. p16 staining was negative.

Diagnosis.
Nose – inverted sinonasal (Schneiderian) papilloma.

Clinical course.
2010 January Well with no nasal obstruction.

Discussion.
There are 3 different types of sinonasal papillomas: inverted, exophytic (everted) and oncocytic.
HPV types 6 and 11 can be identified in about half of exophytic papillomas, not the others. Exophytic papillomas occur most commonly on the septum, whereas the others usually arise from the lateral wall or sinuses. Exophytic papillomas are composed of papillary fronds of squamous or transitional epithelium.
Inverted papillomas show an endophytic growth of hyperplastic ribbons of basement membrane enclosed multi-layered epithelium, 5-30 cells thick. It is usually of non-keratinising squamous or transitional in type. 10-20% show surface keratinisation. 5-10% show varying degrees of dysplasia. They are often associated with oedematous nasal polyps.
Inverted papillomas often recur (about 60% of cases), and are associated with carcinomas in about 10% of cases, usually squamous. Exophytic papillomas should not recur after adequate surgical removal, and are not associated with malignant change.
Case 11 (HI 02-02781).

**Clinical History.**
Female 91 years.
Left nasal obstruction with recurrent epistaxis.

**Microscopic findings.**
Endophytic growth of hyperplastic ribbons of basement membrane enclosed multi-layered epithelium, about 5 cells thick. The cells are tall and columnar and have bright pink cytoplasm. A few surface cilia can be seen.

**Diagnosis.**
Nose – oncocytic sinonasal (Schneiderian) papilloma.

**Clinical course.**
Recurrence 9 months later.
4 years later well. No recurrence.

**Discussion.**
Oncocytic papillomas almost always arise from the lateral nasal wall or the sinuses. They exhibit both exophytic and endophytic growth of oncocytic columnar cells, 2-8 cells thick. The nuclei are usually small and dark. Cilia are often seen on the outer surface.

25-35% of oncocytic papillomas recur, whereas 4-17% of oncocytic papillomas are associated with a carcinoma.
**Case 12 (HI 07-24488).**

**Clinical History.**
Male 57.
Left-sided nasal polyp.

**Microscopic findings.**
Fragments of an intestinal type adenocarcinoma, with focal necrosis and mucin production. There is considerable cytological atypia and mitotic activity. No signet ring cell is seen.

**Immunohistochemistry.**
CK7+, CK20+, CEA+.
Negative: TTF-1, PSA, Synaptophysin.

**Diagnosis.**
Nose: High grade sinonasal adenocarcinoma of intestinal type.

**Clinical course.**
Nov 2007 Polypectomy.
March 2008 left lateral rhinotomy. Upper GI endoscopy was negative.
Possible mediastinal and lung metastases (not confirmed on biopsies), found to be sarcoidosis.
Radiotherapy to nose.
July 2009 well, no recurrence.

**Discussion.**
Adenocarcinoma of the nose can be considered as:
Salivary or non-salivary.
The non-salivary are intestinal or non-intestinal.
All can be either low or high grade.
Case 13 (HI 09-08885).

Clinical History.
Male 83.
6 months L nasal obstruction. Non-smoker.
   MRI: Aggressive tumour of left nose and maxillary antrum, extending into the orbit.
   Also has bilateral cervical node metastases.
2009 Apr biopsy and debulking operation.

Microscopic findings.
Invasive very poorly differentiated carcinoma with no obvious squamous or glandular differentiation.
   Areas of necrosis.
   Considerable cytological atypia and plentiful mitotic figures.

Immunohistochemistry.
Positive: MNF, EMA.
Negative: S-100, pan-melanoma cocktail, p16, synaptophysin, Chromogranin A, EBER.

Diagnosis.
Nose: Sinonasal undifferentiated carcinoma (SNUC).

Further Clinical Information.
2009 April: operation.
   FNA of neck nodes shows carcinoma.
   Palliative radiotherapy.
2009 November good response, particularly of the lymph nodes.
   Further follow up in another hospital.

Discussion.
   Sinonasal undifferentiated carcinoma (SNUC) is highly aggressive carcinoma of uncertain histogenesis. It has a median survival of 18 months. A combination of radical surgery and chemo and radiotherapy may help.
   Recently, a subset has been found with NUT (nuclear protein in testis) gene rearrangement. These also show foci of well differentiated squamous carcinoma. Too few cases have been reported to assess whether it has any better prognosis.
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Case 14 (HI 92-02899).

Clinical History.
Female, born 1907. In early 1992 she presented with a 3 week history of left nasal obstruction, discomfort and bleeding. Examination revealed a smooth grey polyp in the nose.

Microscopic Findings.
Haematoxylin and Eosin.
The specimen comprises fragments of bone, cartilage, soft tissue and sinonasal mucosa with an ulcerating tumour. The degree of cellularity varies from dense to loose. There are no tubules, keratin pearls, rosettes or other structures. The cells vary from small lymphocyte-like to large and pleomorphic, and many have large vesicular nuclei with prominent nucleoli. The cytoplasm also varies from clear to eosinophilic, and very scanty pigment can be identified. There are frequent mitotic figures. No surface junctional component is obvious in these slides.

Special Stains.
Some Perls positive haemosiderin is seen.

Immunohistochemistry.
S-100 - c.50% cells ++. HMB45 +++. Pan melanoma cocktail++, Vimentin++. AE1/AE3 and CD45 tumour cells negative.

Diagnosis.
Malignant melanoma of the nose.

Further Clinical Information.
At operation, the tumour was found to involve the lower septum, the floor of the nose and the lateral wall. As much as possible was excised. One month later the patient was found to have submandibular lymph nodes and received palliative radiotherapy. She died 3 months after that.

Discussion.
The mucosal surfaces of the sinonasal region account for c.1% of all malignant melanomas¹, and melanoma accounts for 2.4% of all nasal malignancies². The sex incidence is equal and the mean age is 64 (range 13-93)³. Melanomas may be found in black patients. Presenting symptoms include epistaxis, mass and/or obstruction. In decreasing order of frequency, the sites are the nasal cavity (especially the anterior nasal cavity and middle or lower turbinates), maxillary antrum, ethmoid sinuses and the sphenoid sinus. They rarely, if ever, involve the nasopharynx or olfactory mucosa higher in the nasal cavity. The typical macroscopic appearance is that of a polyp, often grossly necrotic or haemorrhagic⁴.

Sinonasal melanoma can exhibit a wide variety of histological appearances⁵. It can be composed of small round cells mimicking lymphoma or small cell carcinoma, large cells similar to large cell carcinoma (epithelioid), or rhabdoid cells resembling rhabdomyosarcoma or rhabdoid tumour, or sarcoma-like spindle cells. It can particularly resemble olfactory neuroblastoma (even with poorly formed rosettes), and the differentiation is partly based on the exact location of the
tumour. Melanin pigment may or may not be present. Junctional involvement of the surface epithelium is seen in only about a third of cases. Immunohistochemistry shows positivity for S-100 protein and HMB45, although spindle cell melanomas may sometimes be negative. There may also be spurious staining with cytokeratins. Newer markers such as Mel A, D5 (microphthalmia-associated transcription factor) and especially tyrosinase (T311) are some value, but S100 remains the best.

Mucosal melanomas are aggressive neoplasms. Chemo- or radiotherapy are of little value, and median survival is 18 months. Nevertheless, some patients have long disease free intervals or no further recurrence or metastasis. Poor prognosis has been related to advanced age, size (>30 mm), inaccessibility and delay in diagnosis, but other factors including depth of invasion have not convincingly been correlated with prognosis. Staging systems for other sinonasal tumours do not work for melanoma, and a separate scheme has been proposed (Table 22-1).4

<table>
<thead>
<tr>
<th>Primary tumour</th>
<th>T1</th>
<th>Single anatomical site</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2</td>
<td>Two or more sites.</td>
<td></td>
</tr>
<tr>
<td>Regional lymph node</td>
<td>N1</td>
<td>Any lymph node metastasis.</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>M1</td>
<td>Distant metastasis.</td>
</tr>
</tbody>
</table>

**STAGE GROUPING**

| Stage I | T1, N0, M0. |
| Stage II | T2, N0, M0. |
| Stage III | T1 or 2, N0 or 1, M1. |

**Table 22-1: Proposed staging for sinonasal and nasopharyngeal malignant melanoma.**

**References.**


OXFORD FRCPath Course: Head and Neck Pathology.

Case 15 (HI 01-20488).

Clinical History.
M 89.
2001 Oct Frontal headaches. Bilateral nasal polyps. CT scan shows a large mass on the right involving most of the nasal cavity and adjacent sinuses.

Microscopic findings.
NOTE: The slide out for review has only a limited amount of tumour on it.
The specimen comprises oedematous sinonasal mucosa containing islands of tumour cells, set in a vascular stroma. The tumour cells consist of round to oval, regular nuclei with scanty pale cytoplasm. Mitotic figures are frequent in places. Rare possible rosettes or pseudo-rosettes are noted. There are small amounts of neurofibrillary matrix. No necrosis is seen, but there are a few apoptotic nuclei.

Immunohistochemistry.
Synaptophysin+++. Chromogranin A+++, Vimentin +++, NSE +++
S-100 (only surrounding sustentacular cells).
Desmin, cytokeratins (MNF116, CAM) negative.

Diagnosis.
Nose-olfactory neuroblastoma (grade 2, but mitotic count suggests Grade 3).

Clinical course.
2002 Jan intracranial extension.
Patient offered palliative chemotherapy, but refused.
2003 Dec Sudden onset left-sided weakness.

Discussion.
Olfactory neuroblastoma is a malignant neuroectodermal tumour thought to originate from the olfactory membrane of the sinonasal tract. Patients range in age from 2-90 years, with two peaks in 2nd and 6th decades. The usual site is the upper nasal cavity in the region of the cribriform plate.

Typically the tumours are localised to the submucosa, growing in circumscribed lobules or nests separated by a richly vascularised fibrous stroma. The neoplastic cells have uniform small round nuclei with scant cytoplasm, dispersed chromatin and inconspicuous nucleoli. Nuclear pleomorphism, mitotic activity and necrosis are usually seen only in high grade tumours. The cells do not have distinct borders, and they are surrounded by a neurofibrillary matrix.

The majority of cells express synaptophysin and Chromogranin A, with S-100 reacting just with the surrounding sustentacular cells. About 10% of cases show a few cells staining for cytokeratin.

Prognosis largely depends on clinical stage, in particular the local extent. Therefore, tumours confined to the nasal cavity have a 75-91% five year survival, whereas the comparable figures for those extending beyond the nose and sinuses is 41-47%. Other factors said to be prognostically important include histological grade and the proliferation index.
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Case 16 (HI 00-10356).

History.
Female born 1945. In 1997 she underwent a right nephrectomy for a renal cell carcinoma – it measured 40 mm in diameter (pT1) and there was no vascular invasion. In 1999 she complained of migraine-like headaches and right retro-orbital pain, which she claimed to have had for 10 years. By June 2000 she had developed an unsteady gait and anosmia. CT and MRI scans showed an extensive tumour in the ethmoid and right anterior cranial fossa. At operation, a polypoid mass was found in the ethmoid sinuses; a biopsy was taken.

Microscopic Findings.

Haematoxylin and Eosin.
The ethmoid biopsies show bone and respiratory mucosa with a deposit of tumour. It comprises a generally uniform population of cells, sometimes arranged in fascicles with Schwannoma-like nuclear palisading. Only rare poorly-formed whorls are seen. Most of the cells are spindle shaped, although some are more polygonal. The nuclei are regular, and a few contain vacuoles. Only very occasional mitotic figures are identified.

Immunohistochemistry.
Vimentin ++++. EMA - focal positivity. MIB1-2%. Cytokeratin MNF116, S-100, CD34 – all negative.

Diagnosis.
Ethmoid sinus – meningioma (extension from intracranial tumour).

Further Clinical Information.
In September 2000 an olfactory meningioma was excised. In March 2006, she fell and fractured her nose, but recovered. At her most recent clinical and MRI assessment she was well with no evidence of recurrence.

Discussion.
Meningiomas of the sinonasal tract may permeate directly from the central nervous system and its coverings or occasionally arise de novo from embryologically misplaced arachnoid tissue. The latter are slightly more frequent in patients with neurofibromatosis type II and may be multiple. In one study, 20% of all intracranial meningiomas extended beyond the cranial cavity and 3% secondarily involved the nasal cavity, paranasal sinuses or nasopharynx. Permeation through foramina and pressure necrosis may result in spread from one sinus to another. Sinonasal meningiomas are more frequent in women, but occur at a younger age than intracranial tumours - the mean age is 28. Similar tumours may occur in the ear and temporal bone.

Symptoms include a mass, nasal obstruction, epistaxis, sinusitis, pain, headache, seizure, exophthalmos, periorbital oedema, visual disturbance, ptosis and facial deformity. The mean size is 30 mm diameter, but tumours up to 80 mm have been reported. They may infiltrate the bone and ulcerate the mucosa.

The histological features are identical to primary intracranial meningiomas. The most common variant is meningothelial (syncytial) with whorls of cells and occasional psammoma bodies, but other subtypes (e.g. fibrous, psammomatous, angioblastic) can occur. Occasional
cases with increased mitotic activity and frankly malignant histological features have been described\textsuperscript{8}. Most react with vimentin and EMA and a minority stain with cytokeratins or S-100 protein. Some also express oestrogen (25\%) and/or progesterone receptors (50\%).

The differential diagnosis includes paraganglioma, carcinoma, olfactory neuroblastoma, melanoma, psammomatous ossifying fibroma and angiofibroma\textsuperscript{9,10}.

Complete excision is sometimes difficult, but if surgically possible, it is curative; recurrence may follow incomplete removal. This is often the case if the tumour wraps itself around vital structures, e.g. internal carotid arteries. Two frankly malignant sinonasal meningiomas causing patient death have been described\textsuperscript{8}.

References
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Case 17 (HI 01-06444).

History.
Male born in Hong Kong 1952. He moved to England and was well until March 2001 when he presented with multiple swellings of the right arm, right neck, the lower back and over the left scapula. He also had occasional nosebleeds and deafness of the right ear with an effusion of the middle ear. Examination revealed a polypoid lesion in the nasopharynx, and a 40 mm mass in the right posterior triangle of the neck. He underwent a FNA of the neck mass and a biopsy of the nasopharyngeal mass.

Microscopic Findings.

Haematoxylin and Eosin.
The sections show fragments of nasopharyngeal mucosa including lymphoid tissue. They are invaded by a tumour with a syncytial growth of tumour cells which show relatively little nuclear variation. There are some squamoid areas, but no keratinisation. Many of the cells possess prominent central nucleoli. Mitotic figures are numerous.

Special Stains and Immunohistochemistry.

AE1/AE3++. S-100 and CD45 - tumour cells negative. EBER positive.

Diagnosis.
Nasopharyngeal carcinoma.

Further Clinical Information.
In May 2001 he received radiotherapy and Cisplatin. At his most recent clinical assessment in July 2002 he was well with no evidence of tumour. In May 2004 he developed neck metastases and bilateral local recurrences and returned to Hong Kong in September 2004.

He has relevant family history: a brother died with nasopharyngeal carcinoma 6 months before this patient presented. Also, a sister had previously had a nasopharyngeal carcinoma and was receiving chemotherapy.

Discussion.

Nasopharyngeal carcinoma is defined by the WHO as a carcinoma arising in the nasopharynx. It encompasses squamous cell carcinoma, non-keratinising carcinoma (differentiated or undifferentiated) and basaloid squamous cell carcinoma. Adenocarcinoma and salivary gland-type carcinoma are excluded. There is no mucin production or evidence of glandular differentiation. Electron microscopy shows squamous characteristics such as tonofilaments and desmosomes. These carcinomas are divided into three subtypes: keratinising squamous, non-keratinizing squamous and undifferentiated. The last is commonly referred to as nasopharyngeal (or lymphoepithelial) carcinoma (NPC).

Although NPC is rare in Western white patients of northern European origin, it is much more common in southern Chinese, as well as to a lesser extent elsewhere such as Africa, the Mediterranean region and amongst Eskimos. In China it accounts for 18% of all cancers, and until recently in Hong Kong 1 in 40 men developed NPC before the age of 75. A steady decline in incidence has been noticed in Hong Kong over the past quarter century. It becomes much rarer in second and third generation Chinese people living in the West. It is twice as common in men as women. The aetiology is partly genetic (perhaps related to HLA-A2), but NPC is intimately
associated with Epstein-Barr virus (EBV). In China, NPC occurs most commonly in patients between 30 and 70 years old, but elsewhere it is often seen in younger patients. NPC can present as a metastasis in a neck lymph node, and the diagnosis must always be born in mind, particularly in a patient from a high risk population group. The primary may cause hearing loss or otitis media due to involvement of the Eustachian tube. Most NPCs are located in the lateral walls of the nasopharynx, particularly the fossa of Rosenmüller.

Histologically, the usual type of NPC has an unusual, striking and potentially confusing morphology that has prompted several classification schemes over the years. Light microscopic evidence of squamous differentiation is totally or almost completely absent. The cells are arranged in a syncytial pattern with indistinct cell borders. Nuclei are large and vesicular, and nucleoli are prominent. The tumour cells may be arranged in nests or distributed individually among the reactive lymphoid cells. Some cells may be more spindle-shaped. Crush artefacts are common and may cause diagnostic problems in practice. The inflammatory cell response may include large numbers of eosinophils, as well as epithelioid cell granulomas. Amyloid globules are seen in about 10% of cases.

NPC is said to arise from the surface or tonsillar crypt epithelium and be a variant of squamous cell carcinoma. Immunohistochemically, NPCs stain strongly with broad spectrum cytokeratin stains such as AE1/AE3 and most are positive with CK5/6, CK8, CK13 and CK19, but most are negative with CK7 and CK14. Among other markers, EMA is positive, but S-100, CD45, HMB45 and synaptophysin are negative. HER2 is negative and the C-KIT protein (CD117) is found in >50% of patients. EBV positivity can also be demonstrated in the nuclei.

NPC is particularly radiosensitive, and consequently the outcome is often surprisingly good for such an aggressive-looking neoplasm, and survival rates at 3 and 5 years are 70% and 59%. As may be expected, patients with disease limited to the nasopharynx do better than those in whom it is more advanced.

References.


Case 18 (HI 09-21122).

Clinical History.
Female 47 years.
2009 July dizziness; found to have left otitis media. Treated with antibiotics.
2009 August Eardrum still painful and inflamed.
2009 September red bulge behind tympanic membrane.
   Operation: large polypoid tumour filling left middle ear. Biopsy.

Microscopic findings.
The tumour composed of islands of cells, mostly having a “Zellballen” pattern, although this is not always apparent on HE. There is a double cell population:
1. Principal cells – larger and polygonal.
2. Surrounding rim of elongated sustentacular cells.
   There is some nuclear variation, but no mitotic figure is identified.

Immunohistochemistry.
Inner cells: synaptophysin +++.
Outer cells: S-100 +.
CD31/CD34: highlight vascular network.
Cytokeratins, smooth muscle actin negative.

Diagnosis.
Ear – jugulo-tympanic paraganglioma.

Further Clinical Information.
2009 December further excision (histology shows inflamed granulation tissue, with no further tumour).
2010 January well, although some left hearing loss.

Discussion.
This is defined as “a neoplasm arising from one or other of the paraganglia situated in the vicinity of the jugar bulb or in the medial promontory wall of the middle ear.” Most cases arise in women at any age (range 13-85). Most patients present with conductive hearing loss, and sometimes pain in the ear or facial palsy.

The histology resembles carotid body paraganglioma. Epithelioid, small, uniform cells with finely granular cytoplasm are separated by numerous blood vessels forming zellballen, surrounded by peripheral flattened sustentacular S-100 positive cells. The main cells express synaptophysin and chromogranin A, but not cytokeratin.

Jugulo-tympanic paraganglioma is a neoplasm of slow growth. There is often penetration of bone, but metastases are very rare.
Clinical History.
1946 Born.
2008 January L otitis media.
2008 April CT abnormal “inflammatory” tissue in ear and mastoid.
2008 September cortical mastoidectomy and tympanotomy. Small area of vascular
inflammatory tissue corresponding to high signal on MRI. biopsy.
2008 November L radical mastoidectomy (08-26607)

Main microscopic findings.
The biopsy shows bone and soft tissue containing a glandular tumour. This consists of
tubules, small glands, solid islands and cribriform structures. The cells have single regular round
to oval nuclei, and eosinophilic, slightly granular cytoplasm. There is minimal nuclear atypia and no
mitotic activity. The cytoplasm is eosinophilic and slightly granular.

Immunohistochemistry.
Cytokeratin MNF116 +++.
CK5/6 + (patchy).
p63 focally +.
Synaptophysin +++.
Chromogranin A + (patchy).

Diagnosis.
Ear – middle ear adenoma.

Further Clinical Information.
2008 November, further excision.
2009 June, almost complete hearing loss, but no recurrent tumour.

Discussion.
Middle Ear Adenoma is a benign glandular neoplasm showing variable differentiation along
neuroendocrine and mucin-secreting pathways. It is the same tumour as carcinoid of the middle
ear. The tumour arises anywhere in the middle ear cavity, sometimes extending into the mastoid.
Microscopically, middle ear adenoma is formed by closely packed small glands with a back-
to-back appearance. In places, a solid or trabecular arrangement is present. Sheet-like
disorganised areas can be seen where the glandular pattern appears to be lost. The cells are
regular, cuboidal or columnar and may enclose luminal secretion. Occasionally, the cells may
appear “plasmacytoid”. The small central nuclei rarely contain nucleoli, and show no significant
mitotic activity. No myoepithelial layer is seen. It is now clear that most, and indeed probably all,
middle ear adenomas express neuroendocrine markers.
Most tumours are cured by local excision, but a few cases recur after incomplete surgical
removal.
Case 20 (09-00544).

Clinical History.
Male 71 years.
2008 October, left parotid mass for 18 months, slowly enlarging. Facial nerve intact.
2009 January, partial parotidectomy.

Main microscopic findings.
Sections show a well circumscribed tumour, with a solid and reticular growth pattern. There are trabeculae of tumour cells, but no obvious tubule formation. Most cells are epithelioid, but some are some spindle-shaped. The nuclei are regular, and no mitotic figures are identified. The stroma is generally pale, with no myxoid or chondroid material.

Immunohistochemistry.
CAM5.2 ++++. S-100 ++++. SMMHC focally ++. p63 scanty + nuclei. CK5/6 focally +. ASMA and CK14 both negative. The MIB1 proliferation index is <5%.

Diagnosis.
Parotid – benign myoepithelioma.

Clinical course.
2009 January operation.
2009 March well.
Further follow up at another hospital.

Discussion.
Myoepithelial cells are found in several salivary gland neoplasms. Benign myoepithelioma was first described in 1943, and is included in the current WHO classification. Whether or not it is a genuinely separate biological entity is debatable, but most commentators believe that it represents one end of a spectrum that also includes pleomorphic adenoma and possibly even some basal cell adenomas. Nevertheless, myoepithelioma displays particular microscopic features that pose specific practical problems in identification and differential diagnosis, and on this basis it can be accepted as a separate diagnostic category. It can be defined as a tumour composed entirely or predominantly of myoepithelial cells. Criteria to distinguish a mixed tumour with a predominance of myoepithelial cells from a myoepithelioma are largely subjective: some authors do not accept any ductal differentiation in a myoepithelioma, whereas others permit up to one duct per medium-power field, or a single cluster of ducts. We allow up to 5% of the tumour to be composed of ductal epithelium in an otherwise typical myoepithelioma. With more than this, our preference is to designate such tumors as mixed tumors with myoepithelial predominance. If chondroid or osteoid foci are found, we prefer a diagnosis of mixed tumour, although some authors allow focal chondroid differentiation.

Clinical Features.
The incidence of myoepitheliomas to some extent depends on how strictly the entity is defined. Published figures indicate it accounts for 2.2% to 5.7% of all major or minor benign salivary gland tumours, respectively. However, with better recognition of the full histological
range, the diagnosis of myoepithelioma is now made more often\textsuperscript{6,7}, and they may not be as rare as previously thought. More than 200 cases have been reported\textsuperscript{4-17} of which approximately 48% occurred in the parotid gland, 10% in the submandibular gland, and 42% in the minor salivary glands (especially the palate) or in seromucinous gland sites including the nasal cavity and larynx.

Tumours with a similar morphology have also been described in the skin\textsuperscript{18}, lung\textsuperscript{19}, breast\textsuperscript{20} and soft tissues\textsuperscript{18,21}.

Salivary myoepitheliomas occur approximately equally in both sexes. The patients have ranged in age from 6 to 98 years with a mean age in the early to mid-forties\textsuperscript{12,15}. As with other benign salivary gland tumours, myoepitheliomas most often present as slowly enlarging, asymptomatic masses, usually 10 to 50 mm in diameter.

**Pathologic Features.**

Myoepithelioma is a well-circumscribed or encapsulated tumour. Any capsule is generally better developed in tumours of the major glands, whereas those arising in the palate or other minor salivary or seromucinous gland sites are circumscribed but not usually encapsulated. Microscopically, the neoplastic cells are arranged in sheets, irregular collections, nests, interconnecting trabeculae, or ribbons, giving typical solid, myxoid, reticular, microcystic and cribriform growth patterns. The component cells may be spindle-shaped, plasmacytoid (hyaline), clear, polygonal epithelioid, clear, basaloid or oncocytic\textsuperscript{5,6,22}. In addition, overlap forms may be seen, such as elongated epithelioid cells similar to short, stubby spindle cells. Also, many tumours show more than one growth pattern or cell type. In addition, overlap forms may be seen, so that epithelioid cells may be elongated and thus have a similar appearance to those spindle cells, which are shorter and plumper. Also, many tumours show more than one growth pattern or cell type.

The spindle cell pattern is most frequent and has a predilection for the parotid gland\textsuperscript{8,11}. These tumours are often very cellular, with little intervening fibrous tissue or ground substance, and may be multinodular. The spindle cells are usually arranged in sheets, fascicles, or a swirling interdigitating pattern, and occasionally Schwannoma-like nuclear palisading may be seen. Rarely, the spindle cells can show lipomatous metaplasia\textsuperscript{23}. The plasmacytoid type has a predilection for the palate\textsuperscript{8,11} and the cells are arranged in sheets, sometimes separated by an abundant, loose, myxoid matrix that is predominantly composed of hyaluronic acid. The cells are round, oval, or polyhedral with hyaline eosinophilic cytoplasm and eccentric nuclei, but with only a passing similarity to true plasma cells. Although most authors accept the plasmacytoid cells as myoepithelial, it has recently been suggested that these cells originate from luminal and not myoepithelial cells\textsuperscript{14}. Epithelioid cells are polygonal, each with a usually centrally located nucleus surrounded by variable amounts of pale eosinophilic cytoplasm. Clefts, possibly a fixation artifact, may be seen within groups of epithelioid cells, resembling true lumina. The clear cell variant can occur in both major and minor glands, but is relatively rare\textsuperscript{7}. It is composed of a bland uniform population of epithelioid tumour cells with moderate amounts of clear cytoplasm. Oncocytic change in myoepithelial cells is relatively uncommon, and can involve part or all of a tumour\textsuperscript{25}. Occasionally, groups of basaloid cells resembling a focus of basal cell adenoma may be found within an otherwise typical myoepithelioma. In general, nuclear pleomorphism is minimal, but as in mixed tumours, a mild to moderate degree of nuclear atypia with no associated increase in mitotic or proliferative activity may be noted in occasional myoepitheliomas, particularly in those with oncocytic metaplasia. Benign myoepitheliomas do not usually show necrosis, or more than an isolated mitotic figure, but reparative foci with increased proliferation may follow infarction or trauma, particularly from fine needle aspiration (FNA). The stroma in myoepithelioma may be minimal or abundant and is usually acellular and mucoid, myxoid, or hyalinized. It can occasionally contain mature fat cells\textsuperscript{23}, but the chondroid and osteoid-like matrix commonly seen in mixed tumours is by definition not present in myoepitheliomas. Extracellular collagenous crystalloids are seen in 10-20% of plasmacytoid cell type myoepitheliomas, (as well as sometimes in myoepithelial-
rich mixed tumors); these structures are about 50-100 µm in diameter and consist of radially-arranged needle-shaped fibres composed of collagen types I and III, which stain red with the van Gieson method.

Immunohistochemically, there may be considerable variability of staining within the same tumor and between different tumors. However, almost all tumors express S-100 protein, as well as broad spectrum cytokeratins (e.g AE1/AE3, MNF116), and some keratin subtypes, especially 14. Alpha smooth muscle actin (αSMA) and muscle-specific actin positivity is seen to some degree in most spindle cell myoepitheliomas, but only occasionally in the plasmacytoid cell type in vivo, although they do express them in vitro. Staining for Calponin, Smooth Muscle Myosin Heavy Chain (SMMHC), CD10 and Masp is inconsistent in myoepithelial cells. The nuclear transcription factor, p63 is positive in most benign myoepitheliomas. Glial fibrillary acidic protein and vimentin are also frequently expressed, but are non-specific. New markers including p-cadherin and stratifin (14-3-3σ) may become of value in practice, but have not yet been properly assessed.

Electron microscopic studies have also confirmed both epithelial and smooth muscle differentiation, with desmosomes, pinocytotic vesicles and basal lamina separating tumour cells from adjacent connective tissue and cytoplasmic microfilament arrays, although focal densities are not usually found.

**Differential Diagnosis.**

As discussed above, distinguishing pleomorphic adenoma with a predominance of myoepithelial cells from myoepithelioma is largely subjective, as both are morphological variants in the spectrum of a single biological entity. Myoepithelial carcinoma usually shows invasiveness, necrosis, increased mitotic activity (>7/10HPFs) and a MIB1 proliferative index above 10%. Other differential diagnoses of benign myoepithelioma depend on the predominant cell type. Thus, tumors composed of spindle cells resemble various benign mesenchymal neoplasms and tumor-like lesions, such as nodular fasciitis, solitary fibrous tumor, fibrous histiocytoma, leiomyoma, schwannoma and Kaposi’s sarcoma. The clear cell variant must be distinguished from other salivary gland tumors characterized by cells with clear cytoplasm, including metastatic renal cell carcinoma. Immunohistochemistry is valuable in identifying a myoepithelial phenotype in a problem tumor. In particular, none of the benign soft tissue tumors express cytokeratins, and renal cell carcinoma is S-100 protein negative.

**Treatment and Prognosis.**

Since benign myoepitheliomas are considered to represent one extreme of the histological spectrum of pleomorphic adenoma, the treatment and prognosis are essentially the same as for benign mixed tumour. Patients with these neoplasms should be treated by complete excision that ensures a tumour-free margin, for example superficial parotidectomy; in minor gland sites, this will usually involve surgical excision with a rim of normal surrounding tissue. Neither growth pattern nor cell type appears to carry prognostic significance. Malignant change to myoepithelial carcinoma in a benign lesion has been described, but too little information is available about the percentage of cases involved. However, it is not unreasonable to postulate that it is probably similar to that of benign mixed tumour.

**References.**


Clinical History.

Case 21 (08-18246).
2008 April 3 months swelling L parotid. Soft, mobile, painless.

Main microscopic findings.
The parotid gland contains a partly circumscribed tumour. This displays microfollicular and solid growth patterns. The component cells are mostly serous acinar in type, but there are also smaller numbers of non-descript intercalated duct type cells. There is no major nuclear atypia, but occasional mitotic figures are noted. No necrosis is seen. There is a peripheral lymphoid response with germinal centre formation. The tumour has not been excised.

Immunohistochemistry.
The serous acinar cells contain PASD positive cytoplasmic granules.
MNF116 +++.
MIB1 index – 10%.

Diagnosis.
Parotid – acinic cell carcinoma.

Further Clinical Information.
MRI no residual tumour.
2009 April well.
2009 August well.
2010 Jan Well, no recurrence.

Discussion.
About 90% of acinic cell carcinomas (AcCC) arise in the parotid gland; there is an equal sex incidence and a wide age range, and children may be affected, as is the case here. Whilst serous acinar cell differentiation (PASD positive zymogen granules) is diagnostic for AcCC, the spectrum of growth patterns and cellular features is very variable. Growth patterns include solid, microcystic, follicular and papillary-cystic, and other cell types are vacuolated, hobnail, clear and non-specific glandular and intercalated-duct epithelium. The most useful special stain is PASD. Immunohistochemistry has little role in diagnosis, but MIB1 is a valuable prognostic marker, with tumours having proliferation indices <5% doing much better than those >5%. No grading system based on histological features has been shown to be of value.
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Case 22 (HI05-17718).

**History.**
Female 77 years old. Mass in the left side of the tongue.

**Histopathology.**
Microscopy shows soft tissue, muscle and minor salivary glands of the tongue infiltrated by a partly cystic and partly solid tumour composed of mucus-filled goblet cells, non-keratinising squamous cells and intermediate cells. Groups of tumour cells infiltrate as small nests, and there is also perineural invasion. There is relatively little nuclear atypia and mitotic figures are rare. PASD highlights the mucus production and immunohistochemistry for cytokeratin 14 the squamous differentiation. The MIB1 index is 6%.

**Diagnosis.**
Tongue – high grade mucoepidermoid carcinoma.

**Further Clinical Information.**
The full clinical history is she presented in April 2005 with a 5 month history of an intermittent painful mass in the left neck, level II measuring 20-30 mm. Ultrasound showed enlarged nodes in levels II, III and IV, but major salivary glands were normal. The first FNA was unsatisfactory, but a second one showed mildly atypical cells, with a suggestion of papillary carcinoma of the thyroid. MRI scanning showed a “subtle abnormality in the left side of the tongue”. A lymph node biopsy revealed metastatic mucoepidermoid carcinoma of salivary type.

In September 2005 she underwent a local excision of the abnormal area in the tongue, together with a limited neck dissection. In the lymph nodes (levels II, III, V), 5/13 were positive with some extracapsular spread. Over the next few months, she received radiotherapy (60 Gy in 30 treatments).

In 2008 she developed a local recurrence, and in 2009 a metastasis surrounding the right ureter.

In January 2010, she was admitted to the Hospice.

**Discussion.**
Mucoepidermoid carcinoma (MEC) is “a malignant glandular epithelial neoplasm characterized by mucous, intermediate and epidermoid cells, with columnar, clear and oncocytoid populations”.

It is the commonest primary salivary carcinoma worldwide (Ellis & Auclair 1996), although not in Britain (Eveson et al 1985). There is a wide age distribution with a mean of 45 years, but it can be seen in patients as young as 4 years old (Claros et al. 2002). Interestingly, patients with palate tumours tend to be younger than those with tongue lesions. There is a slight 3:2 female predominance. Approximately half (53%) of cases arise in major glands, mainly the parotid, and the most frequent intraoral sites are the palate and buccal mucosa. Occasionally, MEC arises in minor glands of the nose or larynx and within the body of the mandible. Tumours are usually 10-60 mm in size.

Microscopically, the proportion of the different cell types and their architectural configuration (including cyst formation) vary between tumours and sometimes within any individual neoplasm. Mucous cells tend to be more numerous in MECs with cyst formation.
Mucous cells are cuboidal, columnar or goblet-like and form solid masses or line cysts, where they may be single or multi-layered. The mucin stains with PASD and mucicarmine, and these are particularly useful in cases where mucous cells are few. Mucus-filled cysts may rupture and elicit an inflammatory response. Epidermoid cells usually have intercellular bridges, but it should be noted that the term epidermoid does not indicate squamous differentiation, but simply a squamous-like appearance. Consequently, keratinisation is exceptionally rare in MEC and indeed, the presence of keratinisation should make one doubt a diagnosis of MEC, as it is much commoner as part of squamous metaplasia in pleomorphic adenoma or malignant myoepithelioma, and in metastatic squamous carcinoma from the skin or upper aerodigestive tract. Squamous cells may be sparse in MECs, and high molecular weight cytokeratin stains (e.g. 34\beta E12, CK14, CK5/6) and p63 can help identify them. Intermediate cells are small with dark-staining nuclei and they often form the stratified lining of cysts beneath the mucous cells.

Clear cytoplasm may be seen in either the squamous or intermediate cells, and MEC may take the form of a clear cell carcinoma; similarly oncocytes can be plentiful.

All MECs are malignant with a metastatic potential, regardless of their microscopic appearance. Nevertheless, histological features can be used to predict outcome to some degree, and the AFIP Fascicle proposes that MECs should be put into one of three microscopic grades, based on the extent of the cystic component, neural invasion, necrosis, cytological pleomorphism and mitotic activity. This assessment has considerable prognostic significance, with death rates due to disease of 3.3%, 9.7% and 46.3% for grades 1, 2 and 3 respectively. The present case is grade 1. Recently, a new modified grading system has been proposed. It adds vascular invasion and pattern of infiltration to the AFIP system, and could be more accurate. Assessment of the MIB1 proliferation index has also been shown to be of value (Skálová et al 1994). Expression of different membrane-bound mucins in MECs has shown that MUC1 is related to tumour progression, whereas MUC4 is related to a better prognosis (Alós et al 2005). In addition, molecular methods may have something to offer. MEC can be subdivided into two types on the basis of a recurrent t(11;19) (q21; p13) translocation resulting in a MECT1-MAML2 fusion - i.e. fusion positive or negative. The median survival of MEC patients who were fusion positive was more than 10 years compared to 1.6 years for patients without it (Behboudi et al 2006).

The differential diagnosis of MEC is wide, and includes other primary salivary tumours (e.g. those with clear cells); metastatic squamous carcinoma lacks mucus and generally shows keratinisation; the reactive condition, necrotizing sialometaplasia (salivary gland infarction) comprises mucus glands with squamous metaplasia, but the lobular architecture is preserved and there are no intermediate cells. Adenosquamous carcinoma, a high grade malignancy of epithelial surfaces, also lacks intermediate cells, and shows a more intimate involvement of the surface, sometimes including carcinoma in situ.

References.


Case 23 (HI 09-17682).

Clinical History.
Female 36 years (born 1973).
1995 Left TMJ pain and dysfunction.
2006 December, left parotid mass, 10 mm.
2009 May, slightly larger. FNA showed probable pleomorphic adenoma.
2009 July, MRI showed a mass 14 mm in size.
2009 August, lumpectomy.

Main microscopic findings.
Sections show a tumour with an overall basaloid appearance. It comprises tubules, trabeculae and prominent cribriform structures. The tumour cells are closely packed; there is some nuclear pleomorphism, with visible nucleoli. There is only scanty cytoplasm. Mitotic figures frequent. The cellular structures are separated by hyalinised stroma. Blue myxoid material is seen in some cribriform spaces, and eosinophilic mucus in others. The tumour invades soft tissue, and is present at the excision margin.

Immunohistochemistry.
AB/PAS stains mesenchymal and epithelial mucus differently. CAM5.2++. EMA highlights true epithelial-lined lumina. S-100 focally +; no perineural infiltration. SMMHC stains peripheral cells ++, as does p63++. CK5/6 ++. CD117++. MIB1 index 25%.

Diagnosis.
Parotid – adenoid cystic carcinoma.

Further Clinical Information.
2009 September, superficial parotidectomy, with a small focus of residual tumour.
2009 Oct-Dec, radiotherapy.
2010 January, slightly enlarged neck lymph nodes; otherwise, reasonably well.

Discussion.
Adenoid cystic carcinoma is a basaloid tumour consisting of epithelial and myoepithelial cells in variable morphologic configurations, including tubular, cribriform and solid patterns. It has a relentless clinical course and usually a fatal outcome.

Differentiation from less aggressive neoplasms is important, and whilst this is done mainly on H&E, immunohistochemistry has some value. Pleomorphic adenoma may contain adenoid cystic-like areas, but myxochondroid matrix and plasmacytoid or spindle-shaped myoepithelial cells are usually present. Both adenoid cystic and polymorphous low-grade adenocarcinomas are diffusely infiltrating neoplasms displaying morphological diversity, but can be distinguished cytologically: the former typically have closely packed dark, angular, atypical nuclei and frequent mitotic figures, in contrast to the uniform bland nuclei of the latter. There are some immunohistochemical guides, but with one exception, no absolute discriminants: e.g. S-100 staining is usually more diffuse and stronger in polymorphous low-grade adenocarcinoma, and p63 typically reacts with cells at the periphery of the islands in adenoid cystic carcinoma. CD117 is of uncertain significance and diagnostic usefulness. Much more reliable is MIB1, which is usually <5%
in polymorphous low-grade adenocarcinoma (and pleomorphic adenoma) and >10% in adenoid cystic carcinoma. Basal cell adenoma and adenocarcinoma resemble the solid pattern of adenoid cystic carcinoma, but mitotic and MIB1 indices are much lower. Basaloid squamous cell carcinoma also simulates solid pattern adenoid cystic carcinoma, but lacks any small epithelial-lined spaces and furthermore, the diagnosis requires the presence of a malignant squamous component.

The average 5 and 10 year survival rates are about 60% and 40% respectively, but most patients eventually die of or with their disease. Overall, the main prognostic factors are site (e.g. submandibular worse than parotid), clinical stage and histological pattern. Predominantly tubular and cribriform adenoid cystic carcinomas have a better outcome than tumours with a solid component, especially if this exceeds 30% of the total volume. Another unfavourable feature is the frequent involvement of resection margins, particularly as the result of extensive perineural infiltration. Metastases occur in 40-60% of patients, but unlike other salivary malignancies, adenoid cystic carcinoma metastases tends to involve distant organs (lung, bone and liver) rather than local lymph nodes.
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Case 24 (HI 08-18626).

Clinical History.
Female 69 years.
Mass in the palate.

Main microscopic findings.
Sections show palate mucosa with minor salivary glands and a 2.5 mm long area of tumour, which is not circumscribed and appears to be invasive. It is composed of solid and cribriform structures with a few ducts. The appearance is focally basaloid. The nuclei are regular, with no significant atypia. No mitotic figures are identified there are areas of dense hyaline stroma.

Immunohistochemistry.
CAM5.2++. CK7++. EMA+. S-100++. SMMHC+. p63++. CK 14++. CK 5/6+. CD117 shows focal weak staining only. MIB1 index 2%.

Diagnosis.
Palate – polymorphous low grade adenocarcinoma of minor salivary gland.

Further Clinical Information.
None; follow up at another hospital.

Discussion.
Polymorphous low grade adenocarcinoma is a malignant epithelial tumour characterized by cytological uniformity, morphologic diversity, an infiltrative growth pattern and low metastatic potential. It is the second commonest intra-oral salivary carcinoma. It is more frequent in women and has a wide age range. Most arise in minor salivary glands, particularly the palate, with only rare examples in the parotid.

Cytologically, there is a uniform population of small to medium sized cells with bland, round or oval nuclei, sometimes with intra-nuclear vacuoles and absent or small nucleoli. In contrast, any tumour can encompass several architectural patterns, including ducts, fascicles, micropapillary, cribriform and solid structures. Diffuse infiltration of tumour cells in single file and concentric growth around nerves is reminiscent of lobular breast carcinoma. Mitotic figures are scanty and never atypical. The stroma varies from fibromyxoid to densely hyaline, but the chondroid matrix of pleomorphic adenoma is not seen. The most useful immunohistochemical markers are cytokeratins (broad spectrum, CK7) and S-100 protein. Positivity is also seen with EMA, vimentin, bcl-2 and sometimes with CEA, αSMA and GFAP; MIB1 proliferation is low – mean 2.4% (range 0.2-6.4) in one study.

The most important histopathological differential diagnosis is the much more aggressive adenoid cystic carcinoma [vide supra]. Other considerations include pleomorphic adenoma, often less well circumscribed in minor glands than in the parotid. Any chondroid matrix or circumscription favours pleomorphic adenoma, but it is sometimes impossible to distinguish these tumours on a small biopsy, though both should be excised.

Polymorphous low-grade adenocarcinoma behaves as a low-grade malignancy, with recurrence rates of about 20%, nodal metastases in <10%, distant metastases in <2%, and death...
due to disease in <1%. Long term studies suggest late recurrences and metastases may be more frequent, perhaps due to incompleteness of excision at original surgery.

Papillary structures form part of the spectrum of growth patterns seen in polymorphous low-grade adenocarcinoma, but when extensive, such tumours have slightly more frequent nodal metastases, although the same long-term outlook. Genuine high-grade malignancy occurs rarely, as either a poorly differentiated version of the low grade carcinoma or salivary duct carcinoma.

**Differential Diagnosis.**

*Adenoid cystic carcinoma (AdCC) and Polymorphous Low Grade Adenocarcinoma (PLGA).*

Both tumours are characterised by invasive growth, often with perineural infiltration. There are architectural similarities including tubular, cribriform and solid structures, but in addition, PLGA can display micropapillary, fascicular and whorled patterns. There are marked differences at the cytological level, in that PLGA consists of a uniform cell population with cytologically bland, round or oval and vesicular nuclei and pale eosinophilic cytoplasm, whereas cells in AdCC often appear basaloid and have clear cytoplasm and angular, hyperchromatic nuclei. AdCC also has much greater mitotic and proliferative activity than PLGA.

The importance in the differential diagnosis is that whereas the prognosis is poor in AdCC and characterised by slow relentless growth, patients with PLGA generally do well, and are usually cured by initial excision.
**Case 25 (HI 05-17002).**

**Clinical History.**
Male 62 years (born 1943).
Smokes 20 cigarettes per day.
2004 July Drooping of left side of mouth.
2004 November Numbness of left cheek and ear region for 1 month.
Neurological investigations for facial nerve palsy.
2005 May: MRI showed left parotid tumour.
Patient chose to delay operation.
2009 September Left total parotidectomy and neck dissection.

**Macroscopic findings.**
The specimen consists of a parotid gland 40 × 30 × 30 mm, almost totally replaced by a hard white tumour. There is also an attached supra-omohyoid neck dissection, 90 × 60 × 20 mm.

**Microscopic findings.**
The parotid gland is extensively invaded by a malignant tumour, which reaches the posterior and superior margins of the specimen. The infiltrative component comprises tubules, trabeculae and cribriform structures, and perineural infiltration is widespread. Nuclear pleomorphism is marked and nucleoli are prominent. Mitotic figures are present, but not particularly numerous. There are also in situ lesions with comedo-necrosis.

One of six intra-parotid lymph nodes contains tumour, possibly due to direct spread. There are 11 neck lymph nodes in the neck dissection, all free of carcinoma.

**Special stains and Immunohistochemistry.**
PASD shows a little extracellular mucus.
CK7++. EMA++. GCDFP-15++. Androgen Receptors+++ (80% nuclei; strong intensity). HER2/neu+/++ (i.e. negative). SMMHC, p63 and CK 14 are all negative, but highlight myoepithelial rim of DCIS lesions. S-100, PSA and CK 20 are also all negative.

**Diagnosis.**
Parotid – salivary duct carcinoma.

**Further Clinical Information.**
2005 October Radiotherapy.
2007 August submental lymph node, reactive.
2008 July cervical and thoracic metastases.
2008 August further radiotherapy.
2009 May LHRH analogues.
2009 September looking well, and feeling much better.

**Discussion.**
Salivary duct carcinoma (SDC) was defined in the 2005 WHO Classification as “an aggressive adenocarcinoma which resembles high-grade breast ductal carcinoma”. Previously thought to be extremely rare, it is now recognised as not infrequent, and in Exeter accounts for about 2% of all salivary tumours. Most patients are over 50 years old and there is an at least 4:1
male to female ratio. It arises mainly in the parotid, though cases have been described in the submandibular gland and occasionally in the minor glands. Most cases arise de novo, although some develop as the malignant component of carcinoma ex pleomorphic adenoma, and a single case has been reported arising in (or in association with) a polymorphous low grade adenocarcinoma of the palate.

All histological studies on SDC have noted the strong morphological resemblance to in situ and invasive ductal carcinoma of the breast. The former component comprises expanded salivary ducts with solid, papillary, “Roman bridge”, cribriform and comedo patterns and the infiltrating tumour can include small ducts, cribriform structures, small nests of cells and trabeculae, all accompanied by stromal desmoplasia. Perineural and lympho-vascular invasion are frequent as well. SDC is composed mainly of cells with eosinophilic cytoplasm and often vesicular nuclei containing prominent central nucleoli. Frequently, there is marked nuclear pleomorphism, also apparent on FNA cytology. Mitotic and MIB1 indices are usually high.

In addition to the usual type of salivary duct carcinoma, a few rare morphological variants have been reported: micropapillary, sarcomatoid, mucin-rich and oncocytic, as well as pure in situ cases. In the micropapillary variant, clusters of cells without fibrovascular cores are each surrounded by a clear space, and there is an “inside-out” pattern of EMA staining. The mucin-rich variant includes areas of typical SDC and mucin lakes containing malignant cells. The sarcomatoid type is a composite of usual salivary duct and spindle cell sarcomatoid carcinomas. It may account for some tumours previously classified as carcinosarcoma (“true malignant mixed tumour”). A few oncocytic cells can be seen in any SDC, but a genuine oncocytic variant has only been described in outline, in which most cells in a neoplasm with morphological and immunohistochemical features of SDC show evidence of oncocytic differentiation. Although pure in situ salivary duct carcinoma was not recognized as an entity by the 2005 WHO classification, occasional cases have been described, characterized by an intraductal proliferation of malignant cells, similar to ductal carcinoma in situ of the breast. The diagnosis requires strict criteria, particularly the absence of local invasion, determined by adequate sampling of the whole tumour and the presence of an intact myoepithelial layer around all tumour islands, ideally confirmed by immunohistochemistry.

SDC is mainly an H&E diagnosis and immunohistochemical stains such as androgen receptors (AR) are at present mainly confirmatory, but a combination of molecular and immunomarkers may in future form the basis for subclassification and be therapeutically important.

Given the morphological similarity to mammary ductal carcinoma, a recent study speculated that SDC can be classified into similar molecular subtypes (luminal, HER2+ and basal types) by using a surrogate immunohistochemical panel of a hormone receptor, HER2 and basal/myoepithelial markers, as advocated for a molecular classification of breast cancer. There, the luminal subtype is characterised by positivity for oestrogen receptor (specifically, the α isoform - ERα). Expression of this in SDC is exceptional, but studies have demonstrated androgen receptor (AR) staining in a high proportion of invasive SDCs. Two more recent large series identified that 83% and 67% of cases were AR positive, and in addition, the second of these series showed that 73% of SDCs expressed oestrogen receptor β isoform (ERβ), a receptor in which androgens participate in its regulation. Consequently, it is not unreasonable to postulate that AR expression in SDC is analogous to ERα reactivity in breast carcinoma, and can be used as a marker of the luminal phenotype.

HER-2 protein overexpression has been reported in SDC for some years, but only in 2003 was this more accurately quantified in an immunohistochemical study of several different HER2 protein antisera together with FISH gene analysis. This showed that protein overexpression is usually, but not always (even when 3+) associated with gene amplification. No basal phenotype SDC has been described in detail as such, but one possible CK5/6 positive case
was reported in the German literature\textsuperscript{17,18}, and there was one in our series (reported only in abstract)\textsuperscript{9,10}.

Linking their findings to outcome, Williams et al found that SDCs negative for both AR and ER\textbeta were more aggressive than tumours which expressed one or both of these markers. The same study also found that carcinomas which were HER2 protein 3+ had a worse outcome than those which were HER2 protein 0-2+\textsuperscript{15}.

Extrapolating from these data, it has been suggested that invasive and in situ SDCs could be classified into three main groups (luminal, HER2+ and basal phenotype), based on positive nuclear staining of AR, HER2 protein overexpression (and/or gene amplification) and positive cytoplasmic staining for basal markers such as cytokeratins types 5/6, 14, 17, and epidermal growth factor receptor (EGFR)\textsuperscript{9,10}. In this study the luminal subtype constituted the majority of SDCs and were mostly of low or intermediate nuclear grade. In contrast, the HER2 and basal subtypes were generally of high nuclear grade. The relative percentages for each subtype were 70\% luminal, 15\% HER2, 3\% basal and 11\% indeterminate\textsuperscript{10} - an expanded series of 43 cases has found almost identical proportions (Di Palma et al, in preparation). Therefore, it may be possible to consider targeting different treatments for each different subtype of SDC; for example tumours expressing AR may be eligible for anti-androgen therapy, and those positive for HER2 protein for Trastuzumab (Herceptin).

SDC is one of the most aggressive salivary malignancies. At present, death occurs in 60-80\% of patients, usually within 5 years; about 33\% develop local recurrence and 50\% distant metastases, at sites including lungs, bone, liver, brain and skin\textsuperscript{19}. The outcome for pure SDCIS should be good, provided it is completely excised\textsuperscript{8}.

References.


Case 26 (HI 09-00780).

Clinical History.
Mass on the palate.

Microscopic findings.
Microscopic examination shows soft tissue infiltrated by tumour cells. They are arranged in islands and loosely cohesive sheets. The cells exhibit considerable variation in size and shape, and nuclei are moderately to severely pleomorphic. Most cells have plentiful pink granular cytoplasm, but some are clear. Mitotic figures numerous.

Immunohistochemistry.
MNF116+++. EMA+++. Vimentin+++. CD10+++. RCC negative. Myoepithelial markers (S-100, SMMHC, p63) are all negative.

Diagnosis.
Palate – metastatic renal cell carcinoma.

Further Clinical Information.
History not provided at the time of biopsy.
In 2002, he lived in another part of the country and was found to have a large left renal tumour with metastases in the liver, right kidney and lungs. He was treated with a left nephrectomy and interferon. Subsequent scans showed that the liver lesions resolved, but not those in the lungs. In 2005, he moved to Devon and was followed up in Exeter. The lung metastases had remained stable, but in late 2006, they were noted to have grown again. NHS funding for sunitinib or sorafenib was refused. Interferon was restarted. In 2007, he developed metastases in the right adrenal gland and a portal lymph node. His lung metastases initially stabilised, but began to grow again. During 2008, his condition deteriorated and he developed groin abscesses and Clostridium difficile diarrhoea. In January 2009, he developed a mass on the palate.

Clinical course after biopsy.
Died 10 days after the biopsy.

Discussion.
A metastasis may be the first presentation of renal cell carcinoma, and also, secondaries may present many years after a primary has been removed and apparently successfully treated. Renal cell carcinomas of conventional type are CK7/20 negative, but react with CD10. Other markers (e.g. RCC) are less reliable.
Case 27 (HI 08-05918).

Clinical History.
Female 60 years.
Right throat pain. ? cyst of the larynx.

Microscopic findings.
- Mucosa covered by squamous epithelium containing a localised, non-encapsulated tumour.
- The component cells have small bland nuclei, surrounded by plentiful eosinophilic granular cytoplasm. There is no atypia or mitotic activity.

Immunohistochemistry.
- PAS+D shows only a few cells with positive cytoplasm.
- S-100++. MIB1 index 3%. Cytokeratins (MNF116, AE1/AE3), Pan melanoma cocktail are all negative.

Diagnosis.
Larynx – granular cell tumour.

Further Clinical Information.
No further information.

Discussion.
- Granular cell tumour is a neural tumour composed of round and/or spindle cells with pink granular cytoplasm due to abundant intra-cytoplasmic lysosomes. It has an equal sex distribution and involves a wide age range, but Black patients are said to be affected more often than other races. It occurs throughout the body, but the larynx and trachea are well recognised sites. Most tumours are firm and polypoid or sessile, and less than 20 mm in diameter.
- Microscopically, they are poorly circumscribed and composed of round or spindle cells. The nuclei are small, and there is plentiful eosinophilic cytoplasm which contains PASD positive granules, which also stain for S-100 and CD68. Sometimes, there is pseudo-epitheliomatous hyperplasia of the overlying squamous epithelium.
- Although initial surgery is usually curative, 2-8% of patients may develop local recurrences or second tumours.
Case 28 (NG 09-00212, HI 09-10328).
Clinical History.
1985  hypertension.
1991  MI
1993  stents.
2003  hypothyroidism.
2004  MI.
2007  MI.
2007 iliac, femoral artery ops.
2008 smoking cessation advice.
2009 January well-circumscribed mass L parotid 3 months. FNA.
2009 May     L superficial parotidectomy.
Main cytological findings.
A mixed population of lymphoid cells and sheets of oncocytic epithelial cells. The latter have plentiful granular cytoplasm, and some are orange on the Pap stain. There is no nuclear atypia.

Histological findings.
A well-circumscribed partly cystic mass composed of oncocytic epithelial cells, some of which are columnar in shape. There is a heavy lymphoid infiltrate with germinal centre formation.

Special stains and Immunohistochemistry.
Not required.

Diagnosis.
Parotid – Warthin’s tumour.

Further Clinical Information.
None.

Discussion.
Aspirates from Warthin’s tumour are characterised by the triad of a mixed lymphoid population, sheets and clusters of oncocytic epithelial cells and a dirty proteinaceous background. FNA may produce secondary metaplastic changes in the tumour when seen as a surgical specimen. These can include widespread infarction, heavy inflammation (including granuloma formation) and mature and immature squamous metaplasia, with occasional goblet cells.
Case 29 (NG 09-01704, HI 09-13321).

Clinical History.
2009 April R parotid mass 1 year.
        FNA.
2009 June R parotidectomy.

Main cytological findings.
There is plentiful metachromatic stromal material, which is often fibrillary. There are scattered aggregates of epithelial or myoepithelial cells, which are generally regular. There is a little nuclear variation, but no significant atypia.

Histological findings.
A fairly well-circumscribed mass of myxo-chondroid stromal material with scattered aggregates of myoepithelial cells as well as epithelial-lined ducts. There is no significant atypia or mitotic activity.

Special stains and Immunohistochemistry.
Not required.

Diagnosis.
Parotid – pleomorphic adenoma.

Further Clinical Information.
2009 July good recovery.

Discussion.
FNA characteristically produces cellular islands together with chondromyxoid stroma which appears metachromatic on Giemsa stains. It is typically feathery or filamentous. The cellular component consists of sheets of generally regular epithelioid cells. Nuclei generally are regular, but can show variation in size from time to time. The differential diagnosis includes other tumours with plentiful stroma, such as adenoid cystic carcinoma, and this can be very difficult at times. The cribriform structures in adenoid cystic carcinoma usually have rounded edges.

Malignant change in a pleomorphic adenoma is characterised by cytological atypia.
**Case 30 (NG09-04150, HI 10-01934).**

**Clinical History.**
Male 78 years.
Left neck mass; clinical diagnosis – Warthin’s tumour.
Previous squamous cell carcinoma of the ear.

**Main cytological findings.**
There are numerous mainly cohesive sheets of atypical epithelial cells, most of which have dark hyperchromatic nuclei. There is considerable nuclear variation.

**Macroscopic findings.**
Modified radical neck dissection. There is a 57 mm long white mass in level II.

**Histological findings.**
The large mass is a deposit of metastatic moderately to poorly differentiated non-keratinising squamous cell carcinoma. There is plentiful tumour necrosis. No extracapsular spread is obvious, and there is no desmoplastic stromal response.

*Special stains and Immunohistochemistry.*
Not required.

**Diagnosis.**
Metastatic squamous carcinoma.

**Further Clinical Information.**
Recent case.

**Discussion.**
FNA produces atypical epithelial cells arranged in variably cohesive clusters. Keratinised cells are often elongated resembling tadpoles. In patients with extensive disease who are unsuitable for surgery, FNA may be the only diagnostic procedure performed. The differential diagnosis includes branchial cyst where squamous cells are found, but these do not exhibit the atypia seen here.
MAJOR REFERENCES.


