Genital herpes: a sore subject

I was taught that herpes simplex virus type 1 (HSV-1) causes cold sores on the lip while HSV-2 causes genital sores. But that’s all changing, with HSV-1 fast becoming the leading cause of genital herpes in many countries. According to the World Health Organization, two thirds of the world’s population under 50 years old are infected with HSV-1, and half a billion people aged 15-49 have genital infection due to HSV-1 or HSV-2.

This small prospective cohort study of 82 people with their first episode of genital HSV-1 infection found significant levels of genital viral shedding after the initial infection (12.1% of days in a 30 day period at two months and 7.1% at 11 months) despite antiviral treatment for the initial episode. Prolonged genital shedding was more likely in those who hadn’t encountered HSV before. Counterintuitively, viral shedding was mostly asymptomatic and was rare from genital and oral lesions, so you wouldn’t know to avoid sex unless, like the trial participants, you swabbed your mouth and genitals every day and sent the swabs off for PCR testing.

Back down

Around 30% of people who have lumbar spine surgery for their bad backs experience persistent or even worse radicular pain after their surgery. Spinal cord stimulation for this type of chronic pain is a growing and lucrative market, but there’s not much convincing evidence of its benefits.

In this Norwegian crossover randomised trial of 50 people, two three month periods of bursts of spinal cord stimulation using a subcutaneous implantable pulse generator with leads into the epidural space, resulted in no significant difference in self-reported disability related to back pain, leg and back pain, quality of life, physical activity levels, or adverse events (18%) compared with placebo. However, the placebo effect was powerful, highlighting the need to treat claims made on the basis of open label trials with caution if not scepticism.

The heart of the matter

Allopurinol is great for gout, but does it help the heart? This large, UK, prospective randomised study (ALL-HEART) found that allopurinol (600mg/day) didn’t improve major cardiovascular outcomes in people over 60 years old with ischaemic heart disease (but not with gout) compared with usual care. There was no difference in the number of non-fatal heart attacks, strokes, or cardiovascular deaths over five years. Rates of cancer and adverse events were similar in both groups. Unfortunately, there was a very high dropout rate (57%) in the allopurinol group, which may have skewed results. The results may not be widely generalisable as 99.2% of participants were white, and most participants had had ischaemic heart disease for 10 years or more.

Vitiligo promise

Vitiligo can be stigmatising and distressing, but clinicians have little to offer except sympathy and camouflage creams. Ruxolitinib is a Janus kinase inhibitor that blocks cytokines and reduces inflammation. Can ruxolitinib cream (licensed for use in eczema) help in vitiligo? Two phase 3 trials (TRuE-V1 and V2) found that 1.5% ruxolitinib cream used twice a day resulted in more repigmentation of vitiligo patches than placebo (vehicle controls) over the course of a year (29.8% v 7.4% in TRuE-V1 and 30.9% v 11.4% in TRuE-V2).

It did, however, cause adverse events in over half of the participants, including acne, nasopharyngitis, and itching. Half the patients who applied the active cream from day one had at least 75% facial repigmentation and at least 50% total body repigmentation at one year. Follow-up was limited by the covid-19 pandemic, and most participants were white, which limits generalisability to other skin types.

A for apixaban

Atrial fibrillation (AF) is common in our ageing populations. Over 60% of people with AF also have valvular heart disease (VHD), and both conditions increase the risk of stroke. Anticoagulants reduce the risk of stroke, and direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban have largely replaced warfarin as they’re so much easier to deal with. But how do we choose between the two DOACs?

This cohort study of nearly 20 000 people with AF and VHD registered on a US commercial health insurance database found that apixaban was associated with a lower rate of ischaemic stroke or systemic embolism and bleeding (gastrointestinal or cerebral) compared with rivaroxaban within the first year of treatment initiation (absolute reduction in probability 0.011 and 0.019). There was no difference in all cause mortality between apixaban and rivaroxaban over the seven year study period. The study design meant that variables such as body mass index weren’t captured, which could have contributed to confounding.
A 59 year old man attends his GP describing a three month history of bilateral breast enlargement. He noticed his nipples were painful when the dog jumped up at him, and reports having put on weight and having lost interest in sex. He has also developed difficulties in producing and sustaining an erection over the previous 18 months.

Gynaecomastia is the benign development of male glandular breast tissue. It is a relatively common condition, affecting an estimated one third of men during their lifetime. In the early stages of development, if the cause is identified and treated, the condition is frequently reversible. Among adolescents with physiological gynaecomastia, the condition regresses without intervention in 90% of cases.

The causes of gynaecomastia are physiological or non-physiological (table 1). Physiological gynaecomastia occurs in newborns, adolescents, and older adults. Maternal trans-placental oestrogen transfer has been implicated in the development of neonatal gynaecomastia, and a comparative lag in testosterone secretion during adolescence and declining free testosterone levels in senescence are associated with pubertal and old age presentations. Non-physiological causes include chronic disease, malignancy, and medication or drug use.

### Table 1 | Common causes of gynaecomastia

<table>
<thead>
<tr>
<th>Cause</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological</td>
<td>25%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>25%</td>
</tr>
<tr>
<td>Medication and drug use</td>
<td>20-25%</td>
</tr>
<tr>
<td>Primary hypogonadism</td>
<td>8-10%</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>8%</td>
</tr>
<tr>
<td>Other</td>
<td>7%</td>
</tr>
</tbody>
</table>

**Why do patients present?**

Patients may present to their doctor for a variety of reasons. In this example, the patient presented because of pain. However, pain is not a universal symptom, and for some, anxiety about health or aesthetic concerns may predominate.

**Psychological impact of gynaecomastia**

Patients report feeling anxious, depressed, and emasculated by their symptoms. One report highlighted how men perceived gynaecomastia as a threat to their masculinity. Low self-esteem was another common theme reported in studies that assessed the psychological impact of the condition. Consider how the cosmetic and physiological changes associated with gynaecomastia may affect an individual’s sense of self and how it may be affecting their relationships. Approach this issue sensitively and first ascertain what is most troubling the patient about their condition. This may be anxiety about cancer, aesthetic concerns, pain, or the impact on relationships. Clarifying the patient’s reasons for attending in a neutral and supportive manner may help to guide interventions. Allow yourself to be guided by the patient’s language.
What you should cover

History
Ascertained the onset and duration of symptoms. Rapid onset is more concerning for underlying pathology such as malignancy, whereas chronic cases are rarely a cause for concern.

Use the history to distinguish between the following possible causes:
Physiological—Rarely warrants further investigation. Exceptions include adolescent patients with Klinefelter’s syndrome or when older men experience recent and rapid onset symptoms.
Lifestyle—Greater adiposity increases peripheral aromatase activity, converting testosterone into oestrogen. Consider exogenous sources of oestrogens, such as alcohol, soya foodstuffs, lavender, and tea tree oil.
Drugs—When taking a history, consider recent introductions of medications or a history of drug use. The following are associated with gynaecomastia:

Medications
- Spironolactone, ketoconazole, finasteride, androgen receptor antagonists, GnRH analogues, proton pump inhibitors, histamine antagonists, benzodiazepines, anti-retrovirals, olanzapine, haloperidol, risperidone, metoclopramide, chemotherapy agents, tricyclic antidepressants, opioids, amiodarone, digoxin, metronidazole, ACE inhibitors, and calcium channel blockers
- Non-prescription and recreational drugs
- Anabolic steroids, cannabis, amphetamines, heroin.

Liver and kidney failure—Gynaecomastia is common in liver cirrhosis and among patients undergoing haemodialysis.

Breast cancer and other cancers—Ask about the duration and progression of symptoms and if the patient has any family history of cancer. Inquire about weight loss, night sweats or fevers, and if symptoms are bilateral or unilateral. Unilateral breast symptoms raise the possibility of breast cancer, but this is exceptionally rare, with around 375 cases occurring annually between 2016 and 2018. Breast cancer occurs most commonly in men over 50, with a mean age of 65 at diagnosis. Patients with Klinefelter’s (XXY) are significantly more predisposed to breast cancer, though exact and relative risks vary in the literature. The lifetime risk of male breast cancer has been estimated at 1-5% for men carrying the BRCA1 mutation, and 5-10% for those carrying BRCA2 on a background population risk of 0.1%. Men from sub-Saharan Africa are at higher risk, accounting for 7-14% of breast cancer cases, though the reason for this is not well understood. Additionally, testicular, adrenal, liver, and lung tumours are rare precipitants of gynaecomastia.

Endocrine disorders—Ask about weight loss, weight gain, diarrhoea, tremors, heat intolerance, anxiety, palpitations, sexual dysfunction, libido, visual disturbances, and headaches. Endocrine causes include primary and secondary hypogonadism, hyperthyroidism, hyperprolactinaemia, and Cushing’s syndrome.

Examination
Distinguish between gynaecomastia and pseudo-gynaecomastia (table 2): the latter is caused by excess adipose tissue. When palpated gently between thumb and forefinger, pseudo-gynaecomastia allows the examiner’s fingers to meet at the areola. In a patient with gynaecomastia, this is prevented by the presence of a firm disc of glandular tissue, ≥ 2 cm in diameter. Undertake:
- A bilateral breast examination including axillary and supraclavicular lymph nodes
- A physical assessment for sparse body hair, reduced muscle mass, testicular atrophy, and peripheral stigmata suggestive of hyperthyroidism, chronic liver or kidney disease
- A testicular examination, if there is a clinical history of a lump, pain, or swelling.

Table 2 | Differential diagnoses and their examination findings

<table>
<thead>
<tr>
<th>Gynaecomastia</th>
<th>Pseudo-gynaecomastia</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly bilateral, but may be unilateral, particularly in adolescents</td>
<td>Bilateral</td>
<td>Unilateral</td>
</tr>
<tr>
<td>Pain or tenderness are recognised symptoms, but not universal</td>
<td>Painless</td>
<td>Pain is a rare presenting symptom</td>
</tr>
<tr>
<td>Concentric with the nipple-areola complex</td>
<td>-</td>
<td>May be situated away from the nipple-areola complex</td>
</tr>
<tr>
<td>Firm, rubbery disc of sub-areolar tissue</td>
<td>Texture is consistent with other sources of subcutaneous fat</td>
<td>Hard, fixed, irregular mass</td>
</tr>
<tr>
<td>No overlying skin changes</td>
<td>No overlying skin changes</td>
<td>Skin dimpling, eczematous changes, ulceration, nipple retraction, bloody discharge</td>
</tr>
<tr>
<td>No associated lymphadenopathy</td>
<td>No associated lymphadenopathy</td>
<td>Local lymphadenopathy may be present</td>
</tr>
</tbody>
</table>

RED FLAG SIGNS
Breast cancer
- Unilateral enlargement
- Hard or irregular breast mass
- Painful enlargement >18 months
- Macromastia (5 cm)
- Ulceration or eczematous skin changes
- Nipple discharge/retraction
- Axillary lymphadenopathy

Testicular cancer
- Painless testicular lump
- Asymmetric change in shape or texture

PATHOPHYSIOLOGY
Gynaecomastia is the result of an imbalance of testosterone and oestrogen. Some conditions reduce the circulating amount of active testosterone or increase the amount of circulating oestrogen, while others result in increased peripheral conversion of androgens to oestrogens or cause suppression of the hypothalamic pituitary axis, reducing testosterone production. This relative deficiency of testosterone compared with oestrogen stimulates the development of breast tissue.

EDUCATION INTO PRACTICE
- When would you consider further investigations in a patient with gynaecomastia?
- How do you distinguish between gynaecomastia and pseudo-gynaecomastia on examination?
### When is further testing indicated?
Request blood tests in the presence of compelling examination findings or in the absence of a clear cause. Further investigations are unnecessary in cases of physiological or medication induced gynaecomastia.

The Association of Breast Surgery (ABS) advises investigation of the following:
- Rapid enlargement
- Recent onset in lean men >20 years old
- Persistent, painful gynaecomastia
- Massive gynaecomastia in adolescents
- Persistent gynaecomastia in adolescents (over 18-24 months).

### Biochemical investigations
The ABS recommends that first line blood tests include thyroid stimulating hormone, liver function tests, urea and electrolytes, 9am testosterone, alpha fetoprotein (AFP), and beta human chorionic gonadotrophin (B-hCG). In addition, we suggest including oestradiol as a first line investigation, because raised plasma oestradiol is seen in oestrogen secreting testicular and adrenal malignancies (figure).

If initial investigations are normal or the testosterone levels deranged, request follicle stimulating hormone, luteinising hormone, prolactin, sex hormone binding globulin, and albumin.

Routine breast ultrasound is not recommended; however, patients with clinical findings suggestive of breast cancer require urgent referral to breast clinic.

Patients with a raised oestradiol, B-hCG, or AFP require a testicular ultrasound, and should be referred urgently to urology. If the ultrasound is negative, consider the presence of extra-testicular tumours and seek specialist advice before making further imaging requests.

### Management

**Initial actions**
If recreational drugs or medications are implicated, these may be stopped or switched. Improvement or resolution of symptoms can be expected within a few weeks to months in acute cases. For patients experiencing symptoms of low self-esteem, online self-help resources are available from the Centre for Clinical Interventions and the NHS Inform website.

**Additional referral criteria**
In addition to the breakdown provided in the figure, the ABS advises referral to breast clinic for patients with the following symptoms:
- Painful symptoms for ≥ 6 months with normal blood tests
- Unilateral breast lumps with no clear cause or genetic risk factors (Klinefelter’s).

### Treatment
Tamoxifen 10-20 mg once daily is sometimes offered (though not licensed) in the acute phase of gynaecomastia development. Several cohort studies that investigated the efficacy of tamoxifen in adults and adolescents with gynaecomastia found that symptoms improved or resolved in at least 90% of cases. Despite promising results, side effects include hot flushes, sexual dysfunction, headaches, and fatigue. Evidence links prolonged tamoxifen use to an increased risk of venous thromboembolism. Therefore, tamoxifen should only be prescribed following specialist recommendation.

Over time, glandular breast tissue becomes fibrotic. When fibrosis occurs, surgical intervention is the only treatment that will resolve a patient’s symptoms. Fibrosis usually develops within two years of the onset of symptoms; however, surgery is not routinely offered on the NHS. Indications for surgery include persistent pain or a sustained and significant adverse impact on the patient’s psychological wellbeing.

**Reassurance and further support**
Most commonly, gynaecomastia is a benign condition with no clear cause. Patients with longstanding gynaecomastia, no red flags, and a normal biochemical profile can be reassured of the absence of sinister pathology.

### What you should do

#### When is further testing indicated?
- Request blood tests in the presence of compelling examination findings or in the absence of a clear cause.
- Further investigations are unnecessary in cases of physiological or medication induced gynaecomastia.

#### Biochemical investigations
- The ABS recommends first line blood tests include thyroid stimulating hormone, liver function tests, urea and electrolytes, 9am testosterone, alpha fetoprotein (AFP), and beta human chorionic gonadotrophin (B-hCG).
- In addition, suggest including oestradiol.

#### Management
- **Initial actions**
  - If recreational drugs or medications are implicated, stop or switch.
  - Symptom resolution usually within weeks to months.

- **Additional referral criteria**
  - Painful symptoms ≥ 6 months with normal blood tests.
  - Unilateral breast lumps with no clear cause or genetic risk factors.

#### Treatment
- Tamoxifen 10-20 mg daily is sometimes offered in the acute phase.
- Several studies found symptom improvement in ≥ 90% of cases.

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<table>
<thead>
<tr>
<th>Suggested initial examinations and investigations in primary care.</th>
</tr>
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<tbody>
<tr>
<td>AFP=alpha fetoprotein; B-hCG=beta human chorionic gonadotrophin; FSH=follicle stimulating hormone; LDH=lactate dehydrogenase; LFT= liver function test; LH=luteinising hormone; SHBG= sex hormone binding globulin; TSH= thyroid stimulating hormone; U&amp;E= urea and electrolytes; 2WW= 2 week wait.</td>
</tr>
</tbody>
</table>

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PRACTICE POINTER

Investigating dysphagia in adults

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Dysphagia is a commonly encountered problem affecting one in 17 people in their lifetime.1 It describes difficulties with eating, drinking, and swallowing. In those presenting acutely or to primary care, a detailed history guides the decision about urgency, need, and nature of onward referrals. This article highlights salient points in the history and examination when a patient presents with dysphagia, preliminary investigations, and how these inform onward referral and management.

Dysphagia can be caused by functional or structural abnormalities of the oral cavity, pharynx, oesophagus, or gastric cardia and may be acute or chronic in presentation, depending on the cause. New onset dysphagia requires investigation for oesophageal, and possibly head and neck cancer, but is also associated with a variety of benign diseases (table, bmj.com).

Malnutrition and aspiration pneumonia can be sequelae of dysphagia resulting from benign or malignant causes. These patients usually require care from a multidisciplinary team. Speech and language therapists play a key role in assessing and managing swallowing disorders and should be involved early, alongside the dietetic team if there are concerns about nutritional intake.

WHAT YOU NEED TO KNOW

- New onset dysphagia in adults requires urgent direct access upper gastrointestinal endoscopy (to be done within two weeks); dysphagia associated with head and neck cancer red flags requires a suspected head and neck cancer pathway referral
- In many cases malignancy is not found, but management of benign conditions, such as oesophageal dysmotility or gastro-oesophageal reflux, can be challenging
- Secondary sequelae of benign and malignant dysphagia include malnutrition and aspiration pneumonia: consider early input from dietetic and speech and language therapy teams

HOW THIS ARTICLE WAS CREATED

This article was created and planned using a PubMed search and the expertise of the authors. Authors who regularly encounter patients with dysphagia in practice discussed the salient issues that would be useful to most practitioners, and reviewed current literature and guidelines.

How common is dysphagia?

Because dysphagia may manifest as a singular symptom or as one of a collection, the prevalence is uncertain. However, it is more common with ageing and is estimated to affect up to 50% of nursing home residents,2 3 68% of those in care homes with dementia,4 and 40-70% of people who have had a stroke.5

Dysphagia is seen in 10% of older people admitted to hospital acutely. More than 90% of those with motor neuron disease, up to 41% of those with Parkinson’s disease, and 33% of patients with multiple sclerosis develop swallowing difficulties.6

Dysphagia is reported in 27% of people with chronic obstructive pulmonary disease (table, bmj.com).7

Assessing a patient with dysphagia

A 57 year old man complains of difficulty swallowing associated with a sensation of a lump in the throat. He has hypertension and type 2 diabetes. He has never smoked and drinks eight units of alcohol a week. He works as a hospital porter and lives with his wife, who is well.

The case presentation is a common one. When taking a focused history, establish whether this is acute, chronic, or an acute on chronic presentation, and whether symptoms are progressive or intermittent, to inform onward management. The immediate priority is to establish the safety and efficiency of the patient’s swallow and their nutritional status.

Differentiate true dysphagia from persistent throat symptoms, such as repeated throat clearing, cough, mucus in the throat, or catarrh, throat discomfort, and the sensation of a lump in the throat (globus), which has a lifetime population incidence of more than 40%.8 The presence of blood in the mouth or otalgia with the concurrent sensation of a lump in throat are associated with head and neck cancer. Intermittent hoarseness and sensation of a lump in the throat are negatively associated with head and neck cancer.9

What can you eat and drink?

Establish whether the person’s fluid and dietary intake is adequate and meets their daily requirements; weight loss is a strong indicator of insufficient calorie intake. If they are not meeting their daily requirements, an urgent referral for dietetic and medical assessment may be required. Inquire about the differences when ingesting solids and liquids. Patients with a structural abnormality, such as an oral or pharyngeal cancer, may find liquids easier to swallow than solids and may have made dietary adaptations to accommodate their dysphagia. Further, their sensation of a lump in the throat is always present. In globus, the sensation of a lump in the throat is present...
when swallowing saliva but typically subsides when eating and drinking. Patients with vocal cord palsy secondary to head and neck, lung, or breast cancer may describe difficulty with liquids more than solids, and have a higher risk of aspiration. In achalasia, dysphagia to liquids is characteristic.

What happens when you eat and drink?
Consider this in terms of the different phases of the swallow (fig 1).

1. Oral phase: bolus preparation
Begin by establishing whether the patient can chew adequately. Poor dentition, ill fitting dentures, severe gum disease, xerostomia, or temporomandibular joint dysfunction may impair bolus preparation.

2. Pharyngeal phase: propulsion of food to the oesophagus and protection of the airway
Structural lesions or lower cranial nerve dysfunction may impair the pharyngeal phase of swallowing. Throat clearing, coughing, or a “wet” or bubbly sounding voice after swallowing raise concerns for aspiration. Aspiration does not point towards a specific diagnosis, but needs to be included as recurrent chest infections, pneumonia, and even death are potential consequences.

Refer to speech and language therapy promptly if you have concerns about safety of a patient’s swallow. Consider dietary modifications with thickened fluids and/or admission for non-oral feeding. Foul smelling oral regurgitation of food is often described with a pharyngeal pouch.

3. Oesophageal phase: passage of food through the oesophagus
Problems with the oesophageal phase of the swallow tend to cause slow passage of food through the oesophagus, obstruction, or regurgitation, of which aspiration may be a consequence. Ask the patient about food or tablets sticking and whether they have had treatment for this in the past. A long standing history, particularly associated with liquids and solids in equal measure, suggests oesophageal dysmotility and a disparity may exist between patient symptoms and results from investigations. Investigations may be reassuring but symptoms may substantially impair quality of life. Eosinophilic oesophagitis, gastro-oesophageal reflux disease, and achalasia are all benign conditions that may cause dysphagia.

Where do you feel difficulty with your swallow?
The site of the sensation of the holdup can sometimes localise the site of the problem. A suprasternal sensation may be suggestive of a pharyngeal problem and a retrosternal sensation suggestive of an oesophageal problem. This lacks specificity, however, as symptoms felt at the sternal notch may reflect obstruction at the lower oesophageal sphincter. In the absence of coexisting signs or symptoms that localise the problem, this description should not be used to inform where the patient is referred. In most cases, where urgent direct access upper gastrointestinal endoscopy is available, this should be the first investigation.

How long have you had this problem for? Is it getting worse?
A short history (of weeks to months) is more concerning for malignancy. Fluctuating symptoms, or those that have persisted for years, are more likely to be caused by oesophageal dysmotility.
Box 2 | Red flag symptoms for oesophageal cancer that should prompt urgent referral (≤2 weeks) for upper gastrointestinal endoscopy

- Dysphagia or
- Aged 55 and over with unintentional weight loss and any of the following:
  - Upper abdominal pain
  - Reflux
  - Dyspepsia

Ask about other red flag symptoms for oesophageal and head and neck cancer (box 1, box 2). Note that dysphagia is listed on both lists of red flags—use the history, examination, and presence of other red flags to guide initial referral.

Medical history
Ask about a history of:
- **Head and neck cancer or surgery to the head or neck**—resection of head and neck cancers can impair swallowing by leaving a structural deficit, or causing nerve injury that impairs motor function of swallow or sensation within the upper aerodigestive tract.
- **Radiotherapy (to the head, neck, or chest)**—radiation mucositis acutely impairs swallowing because of pain and impaired aerodigestive tract sensation. Xerostomia, fibrosis and rarely, lower cranial neuropathy are late radiation effects causing mild to profound dysphagia.
- **Stroke or neurodegenerative conditions**—dysphagia is very commonly reported in those with stroke and some neurodegenerative disorders (table, bmj.com).
- **Barrett’s oesophagus and achalasia**—both are also risk factors for adenocarcinoma and squamous cell carcinoma of the oesophagus.
- **Congenital or developmental conditions**—such as cleft lip and palate and cerebral palsy—these patients may have problems with swallowing and this can place them at a higher risk for aspiration. Individuals with autistic spectrum conditions and/or learning disabilities are more likely to have sensory motor and coordination difficulties that can result in dysphagia, at any stage of the swallow.
- **Chronic respiratory disease (eg, chronic obstructive pulmonary disease) or recurrent chest infections**—can disrupt the respiratory-swallow cycle, increasing the risk of aspiration. Steroid inhalers can give rise to oral/oropharyngeal candidiasis, and this may be excluded by simple oral examination. Recurrent chest infections may indicate silent aspiration. These may or may not be symptomatic and are caused by motor impairment of swallow, sensory impairment in the upper aerodigestive tract, or a combination of the two, as is often seen in stroke, neurodegenerative conditions, or as a late effect of radiotherapy.

Social history and risk factors
Social history is important, as tobacco and alcohol consumption are independent risk factors for head and neck, and oesophageal cancers. Paan (betel nut) chewing, seen in some patients from South Asia, is a risk factor for head and neck cancer. Oncogenic human papillomavirus (HPV-16 and 18) has emerged as an independent risk factor for oropharyngeal cancer in recent decades, giving rise to predominantly tonsillar and tongue base squamous cell carcinomas in younger non-smokers.

Examination
Examination in primary care may identify the source of the problem, such as a lesion in the oral cavity or a neck lump prompting referral on the head and neck suspected cancer pathway, rather than for urgent direct access upper gastrointestinal endoscopy. Without specialist equipment it is only possible to examine the oral cavity, neck, and abdomen.

Begin by asking the patient to remove dentures if present.

Ask the patient to open their mouth and inspect the buccal mucosa, oral tongue, gingivae, palate, tonsils, tonsillar pillars, and posterior pharyngeal wall for masses, ulcers, leucoplaikia, erythroplakia, gingivitis, and candida.

- Asymmetry or ulceration of the tonsils is concerning for malignancy, especially if present with cervical lymphadenopathy.
- Note oral hygiene, dryness of the mucous membranes, or drooling. Halitosis may be observed with a pharyngeal pouch or head and neck cancer.
- Palpate the cervical lymph nodes in a systematic fashion. Cervical lymphadenopathy is an abnormal finding in adults and warrants a high degree of suspicion. Head and neck and oesophageal cancers may be associated with regional spread to the cervical lymph nodes. Patients with HPV positive oropharyngeal cancer typically present with cervical lymphadenopathy prior to other signs or symptoms.
- Palpate the supraclavicular fossae and thyroid gland.

General
- Assess the patient’s nutritional status: look for loose fitting clothing and evidence of cachexia; record the patient’s weight.
- Voice and speech can be simultaneously assessed during the history taking. Listen for hoarseness, “hot potato” voice (a muffled voice akin to speaking with hot food in the mouth), a weak cough or hypo- or hypernasal speech, which may be seen with tonsillitis or other acute infections in the head and neck, laryngeal or oropharyngeal tumours and dysarthria, which may be seen with oral cancers or neurological disorders.
- Perform a respiratory examination and listen for additional respiratory sounds, such as stridor. Hoarseness may result from laryngeal or hypopharyngeal cancers or vocal cord palsy owing to recurrent laryngeal nerve dysfunction. This may be idiopathic, iatrogenic following neck or intrathoracic surgery, or by direct infiltration by cancers in the neck or chest.
Abdominal examination
Abdominal examination of patients with dysphagia is usually normal; however, this should be performed to exclude abdominal masses and organomegaly and is especially important in those with associated abdominal pain.

Otoscopic examination
Persistent unilateral otalgia with normal ear examination is concerning for head and neck cancer. This is a referral criterion for suspected HNC in some regions.

Neurological examination
Neurological examination is indicated if the patient also has symptoms of stroke or you have concern that there is a neurological cause for their dysphagia. Assess for impairment of the lower cranial nerves (IX, X, XI, and XII) from bulbar, pseudobulbar palsy, or progressive supranuclear palsy. Stimulation of the gag reflex is highly unpleasant for patients and bears little relation to swallowing function, so it is preferable to inspect the soft palate, asking the patient to say “ah.” Asymmetrical elevation of the soft palate or deviation of the uvula from the midline are suggestive of a vagus nerve lesion. The uvula will deviate away from the side of the vagus lesion. Inspect the tongue at rest, then get the patient to protrude, noting any asymmetry. Atrophy or fasciculations of the tongue may be an early indicator of motor neuron disease, which is associated with progressive dysphagia.

Investigations in primary care
Investigations in primary care should not delay urgent referral on the suspected cancer pathway for patients with oesophageal or head and neck cancer red flags, including dysphagia. A full blood count, urea and electrolytes, and liver function tests are helpful to the secondary care team in guiding subsequent investigations. Computed tomography imaging of the chest and abdomen is helpful for those with upper gastrointestinal symptoms and weight loss; however, the availability of and access to investigations differs between regions, and particularly for those with symptoms more suggestive of head and neck cancer, it is best to leave urgent imaging to be arranged by the specialist team if it is likely to delay referral. A chest x-ray image should be requested at the same time as a referral if the patient has complained of persistent hoarseness, to investigate for lung cancer.

Specialist referral
Urgent upper gastrointestinal endoscopy (within two weeks) is the first investigation in most cases (fig 2, bmj.com). A referral via the head and neck cancer pathway is indicated for patients with red flags that suggest an oral or malignant cause, as indicated by the history and examination (box 1). Referral to speech and language therapy is usually made in secondary care, once initial investigations have been performed.

Upper gastrointestinal investigations
Nearly all patients presenting with red flag symptoms associated with oesophageal cancer require an upper gastrointestinal endoscopy, and this may be the only investigation initially required if dysphagia is the only symptom. Those with accompanying weight loss will also require a computed tomography scan. Epigastric discomfort is a common symptom in patients presenting with oesophageal cancer (associated with 70% of cases), but any of dysphagia, nausea, reflux, and anaemia merit further investigation. Oesophageal manometry is the gold standard investigation in patients with oesophageal motility disorders, and would be arranged by specialist teams.

Ear, nose, and throat investigations
Flexible pharyngo-laryngoscopy is performed to exclude pathology in the pharynx and larynx. Pharyngo-laryngo-oesphagoscopy (performed under general anaesthetic) allows better visualisation of the pharynx and larynx and for biopsies to be taken. The distal oesophagus is not visualised. With upper gastrointestinal endoscopy, head and neck cancers may be missed, as the pharynx and larynx are not closely inspected. Trans-nasal oesphagoscopy, increasingly being used in ear, nose, and throat outpatient clinics, enables visualisation and biopsy of both the pharynx and oesophagus under local anaesthetic. Ultrasound and/or fine needle aspiration or core biopsy are used to investigate neck lumps. A high resolution contrast computed tomography image of the neck and chest is required to stage patients with head and neck cancer, but these are usually arranged by specialist teams after referral. A magnetic resonance imaging scan of the neck may be required if dental amalgam artefacts obscure the oropharynx. The cross-sectional imaging modality used differs between units based on local expertise and preference. A barium swallow provides luminal assessment and is helpful in diagnosing cricopharyngeal dysfunction, pharyngeal pouches, and in assessing oesophageal motility. In the context of new onset dysphagia, this should only be used in secondary care after malignancy has been excluded. Functional endoscopic evaluation of swallowing or video fluoroscopy may be performed by a speech and language therapist following clinical assessment.

Competing interests: None declared.

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CASE REVIEW

An acutely painful, hot, swollen knee

A woman in her 90s presented to the emergency department with shortness of breath, fever, and pulmonary oedema, and was admitted for treatment of community acquired pneumonia and heart failure syndrome with doxycycline, furosemide, and oxygen. She had a medical history of respiratory infections, knee osteoarthritis, and gout (for which she was taking allopurinol). She had no joint replacements.

Two days later, her temperature spiked at 38.3°C on the ward. Examination revealed an acutely warm, tender, and swollen left knee with moderately limited flexion and extension and an effusion. No trauma had occurred on the ward. She was otherwise systematically well. Blood tests showed raised inflammatory markers compared with admission (table), but normal renal and liver function, and no derangement of electrolytes. The table also shows the results of the microbiological investigation of the 25 mL of yellow, viscous fluid removed by diagnostic joint aspiration and blood culture.

A plain radiograph of the left knee was taken (figure).

1 What are the differential diagnoses?
2 What is the most likely diagnosis?
3 How would you manage this condition?

Submitted by Jennie Han, Sarah Dyball, Anintitha Boon-Itn, and Mark Taylor
Patient consent obtained.

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1. What are the differential diagnoses?
   • Septic arthritis—most important differential to rule out
   • Crystal arthropathy—gout flare, acute calcium pyrophosphate (CPP) crystal arthritis
   • Trauma
   • Haemarthrosis
   • Osteoarthritis flare
   • First presentation of underlying autoimmune inflammatory condition (such as reactive arthritis, rheumatoid arthritis, psoriatic arthritis)

2. What is the most likely diagnosis?
   Gout (confirmed by the negatively birefringent, needle-shaped monosodium urate crystals on joint aspirate microscopy and negative culture) and acute CPP crystal arthritis (confirmed by the positively birefringent, rhomboid-shaped calcium pyrophosphate crystals).

3. How would you manage this condition?
   Acute gout—A non-steroidal anti-inflammatory drug (NSAID) with a proton pump inhibitor for gastric protection, or oral colchicine.
   If NSAIDs or colchicine are not tolerated, consider intra-articular corticosteroids for monoarticular or oligoarticular attacks, and oral or intramuscular corticosteroids for polyarticular attacks.
   Acute calcium pyrophosphate arthropathy—Ice packs, temporary rest, joint aspiration, and intra-articular injection of long acting corticosteroid. NSAIDs and low dose oral colchicine can be effective, but are limited by side effects, especially in older patients. Avoid corticosteroids in this case.

Relevant laboratory investigations

<table>
<thead>
<tr>
<th>Property</th>
<th>Admission</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count ×10⁹/L</td>
<td>6.3</td>
<td>9.3</td>
</tr>
<tr>
<td>C reactive protein (mg/L)</td>
<td>42.9</td>
<td>106.8</td>
</tr>
<tr>
<td>Blood culture</td>
<td>No growth</td>
<td>No growth</td>
</tr>
<tr>
<td>Synovial fluid microscopy</td>
<td>—</td>
<td>No organism on Gram stain, presence of negatively birefringent needle-shaped crystals and positively birefringent rhomboid-shaped crystals</td>
</tr>
</tbody>
</table>

**Learning Points**

- In order to diagnose and exclude gout, full blood count, ESR, CRP, and negative blood cultures should be requested. Antinuclear antibodies and rheumatoid factor should also be assessed.
- Osteoarthritis is the most common cause of knee pain in older adults. MRI is the most sensitive imaging investigation, but can be challenging in this case.
- Calcium pyrophosphate deposition disease is a common cause of knee pain in older people. It is diagnosed by synovial fluid aspiration and microscopy.
- The use of antibiotics for joint aspiration is controversial, but should be considered in patients with fever and joint pain.
- Patellar tendinitis is a common cause of knee pain in older adults. It is diagnosed by clinical examination and ultrasound.
- The differential diagnosis of knee pain in older adults includes a wide range of conditions, including ligament injuries, meniscal tears, and synovial effusion.
- The use of corticosteroids for knee pain in older adults is controversial, but can be effective in certain cases.
- The use of opioids for knee pain in older adults is controversial, but can be effective in certain cases.
- The use of NSAIDs for knee pain in older adults is controversial, but can be effective in certain cases.
- The use of rehabilitation for knee pain in older adults is controversial, but can be effective in certain cases.
- The use of surgery for knee pain in older adults is controversial, but can be effective in certain cases.
- The use of knee braces for knee pain in older adults is controversial, but can be effective in certain cases.

**Patient Outcome**

Intra-articular methylprednisolone was administered on the ward owing to its rapid onset and the multimorbidity of our patient, relatively contraindicating oral therapies. The next day, she had no more pain, and her knee “has not felt this good since the first day she was in hospital.”

Her community acquired pneumonia settled with antibiotics, and she had no breathing problems on discharge. She had no further exacerbations of crystal arthropathies after 12 months of follow-up.

**Learning Module**

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.
Systolic blood pressure
A meta-analysis of a vast amount of data from randomised controlled trials and cohort studies reports a strong and continuous dose-response relation between levels of systolic blood pressure and risk of ischaemic heart disease over the range 100 to 200 mm Hg. This puts paid to ideas of a J shaped curve where low blood pressure levels are harmful, and to the notion that a threshold separates hypertension and normal blood pressure. A level of 130 mm Hg, for example, was found to carry an 80% increase in the risk of ischaemic heart disease compared with a pressure of 100 mm Hg (Nat Med doi: 10.1038/s41591-022-01974-1).

Mistletoe
The sticky goo in mistletoe berries, viscin, helps the dispersal and propagation of the plant by clinging to the beaks of birds that eat the berries and the bark of the trees that they wipe their beaks on. Viscin also adheres strongly to synthetic materials such as plastics, metals, and glass, and is involved in lipid metabolism, cell differentiation, sebum production, and inflammation—which makes it a good place to start when developing new treatments for acne vulgaris. A double blind randomised study of the topical application of a PPARγ modulator reports encouraging results. Once daily application for three months reduced lesion counts by more than half (Br J Dermatol doi: 10.1111/bjd.21663).

Stroke in pregnancy
Among 6 million women in France aged 15 to 49 who gave birth between 2010 and 2018, the incidence of ischaemic stroke was no higher than in women who weren't pregnant. By contrast, the incidence of haemorrhagic stroke was slightly higher in pregnancy, and the risk of cerebral venous thrombosis was eight times higher. The greatest risk of cerebral venous thrombosis occurred in the peripartum period (Neurology doi: 10.1212/WNL.000000000000200944).

Screening for thyroid dysfunction
Older people presenting with fatigue and malaise are often tested for thyroid dysfunction. But tests based on thyroid stimulating hormone (TSH) levels are so sensitive that they frequently lead to further rounds of testing, continuing follow-up, and even unnecessary hormone supplements. The answer, according to a retrospective investigation in primary care, is to stop measuring TSH and rely on free thyroxine levels instead (Age Ageing doi: 10.1093/ageing/afac215).

Acne
The peroxisome proliferator-activated receptor-γ, commonly known as PPARγ, is involved in lipid metabolism, cell differentiation, sebum production, and inflammation—which makes it a good place to start when developing new treatments for acne vulgaris. A double blind randomised study of the topical application of a PPARγ modulator reports encouraging results. Once daily application for three months reduced lesion counts by more than half (Br J Dermatol doi: 10.1111/bjd.21663).

Research funders should stop worrying about novelty and redirect their focus to utility
Bodies that fund scientific research should stop worrying about novelty and redirect their focus to utility. It would be better to encourage research programmes that lead to tangible benefits and safer lives and ignore publication metrics and prizes. Of course, there’s still a place for curiosity driven research. But the idea that findings from basic research automatically translate into an application for solving human problems is usually wrong (Nature doi.org/10.1038/d41586-022-03131-7).

Invasive procedures and infective endocarditis
A few weeks ago, this column mentioned a case-crossover study in the US that reported a strong temporal association between infective endocarditis and recent dental procedures. A similar approach using data from about 15 000 hospital admissions for infective endocarditis in England also links invasive procedures (such as pacemaker implantation, dental extraction, gastrointestinal endoscopy, and bronchoscopy) to infective endocarditis. It may be time to re-evaluate recommendations about antibiotic prophylaxis for people at high risk (Heart doi: 10.1136/heartjnl-2022-321519).