The appendix: a spectrum of benign and malignant disease

This article discusses the radiological appearances and subsequent management of a diverse spectrum of benign and malignant appendiceal pathologies, including those masquerading as acute appendicitis.

The vermiform appendix is a thin blind-ending tube that originates from the posteromedial aspect of the caecum, with a highly variable anatomical position. It arises from the convergence of three taenia coli, which typically occurs approximately 2 cm inferior to the ileocaecal valve. Although there is considerable individual disparity, the average reported length ranges from 5–10 cm. There have been five well-characterized anatomical positions: retrocaecal, pelvic, paracolic, pre-ileal and post-ileal, with the retrocaecal position regarded as the most common in adults (Ahmed et al, 2007).

The function of the appendix is unclear. It is thought that as a vestigial structure, it initially functioned to aid digestion and involuted through the course of human development into the modern day remnant. However, newer theories have postulated that it is in fact a highly evolved lymphoid organ, which regulates gut luminal immunological homeostasis (Laurin et al, 2011).

Because of its narrow opening into the caecum, the appendiceal orifice is prone to obstruction, which can be caused by a variety of benign and malignant pathology. Once obstructed, the appendix fills with mucinous secretions, with the associated proliferation of gut bacteria (*Escherichia coli*). As luminal pressure exceeds venous capillary pressure, the continuing arterial supply causes congestion leading to mural oedema, inflammation and, in advanced cases, perforation.

The lifetime incidence of appendicitis is 6%, with a slightly higher male preponderance, and 28 years the mean age at presentation. A UK paper demonstrated a 1.96% rate of significant unexpected findings (other than simple appendicitis) on appendectomy specimens, which in conjunction with the large numbers of cases performed each year, is a substantial figure (Jones et al, 2007).

Clinically, appendicitis presents with colicky central abdominal pain that migrates to the right iliac fossa. Associated symptoms include anorexia, nausea and vomiting. On examination, there may be tenderness in the right iliac fossa or rebound tenderness signifying localized peritonism and the patient may be pyrexial. Biochemical markers include leukocytosis or left shift of the full blood count (neutrophilia). These eight clinical and biochemical parameters form the basis of the Alvarado score, which is a 10-point clinical scoring scale with higher scores being predictive of acute appendicitis.

The differential diagnosis of right iliac fossa pain is wide, including renal, gynaecological, colonic and other solid organ pathologies. This can pose a diagnostic quandary. Bowel-related pathology that can mimic acute appendicitis includes both inflammatory and infective disorders such as mesenteric adenitis, terminal ileitis (Crohn's disease, ulcerative colitis), infective colitis, and typhlitis following chemotherapy. Important gynaecological pathologies include ectopic pregnancy, pelvic inflammatory disease and ovarian torsion. Renal tract conditions, e.g. obstructing right-sided calculus or urinary sepsis, should also be excluded. Less commonly cholecystitis and peptic ulcer disease can cause symptoms that localize to the right iliac fossa.

Normal appendix

On ultrasound, identification of the appendix is highly operator dependent, and the normal appendix may not be identifiable, becoming more conspicuous when inflamed. When visualized, the appendix is seen as a blind-ending tubular structure arising from the caecal pole.

The normal appendix is reliably characterized using computed tomography and usually has a luminal diameter of <6 mm and a mural thickness of <3 mm (*Figure 1*).

Benign or classical appendicitis

The appendix is lined with lymphoid tissue, and the most frequent cause of appendiceal obstruction is lymphoid hyperplasia, resulting from cellular proliferation secondary

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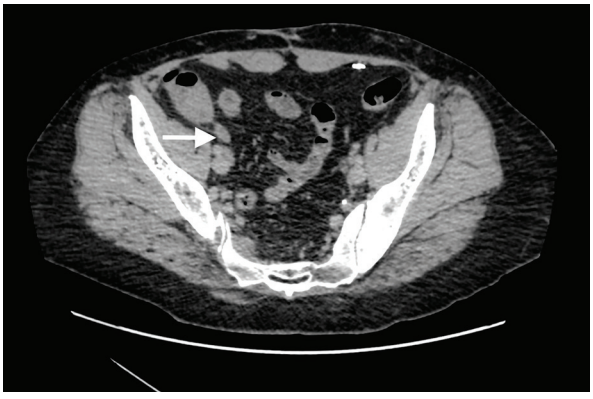


Figure 1. Axial contrast-enhanced computed tomography demonstrates a non-dilated, non-inflamed tubular blind-ending structure arising from the caecal pole, in keeping with a normal appendix (arrowed).

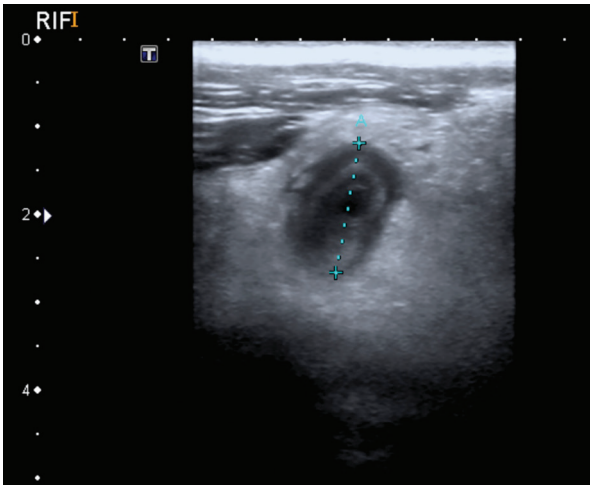


Figure 2. High resolution ultrasound demonstrating acute appendicitis; appendiceal dilatation, oedema of its wall resulting in the 'target sign' and adjacent fat stranding. Note the calipers (A) which indicate an appendiceal diameter of >6 mm.

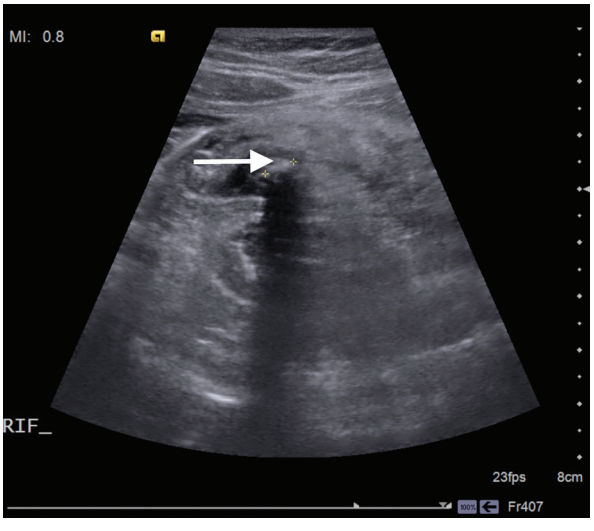


Figure 3. High resolution ultrasound demonstrating an appendicolith (arrowed) as an echogenic structure with acoustic shadowing, within the lumen of the appendix.

to an infective or inflammatory cause. Once inflamed, the appendix may be identified on ultrasound as a non-peristalsing, dilated tubular structure measuring >6 mm in the right lower quadrant, with hyperechoic mucosa, low reflectivity muscular layers, and hyperechoic serosa giving rise to the 'target' sign in axial section (*Figures 2* and *3*). In addition, there may be 'fat wrapping' of the appendix, seen as echogenic fat surrounding the dilated appendix. A peri-appendiceal collection may be found, which indicates localized perforation. The patient may be focally tender in the right iliac fossa on interrogation with the ultrasound probe, demonstrating a positive 'sonographic McBurney's sign'. The graded compression technique aids the ultrasound identification of appendicitis whereby a high frequency linear transducer is used with gradual pressure applied to the right lower quadrant to displace adjacent loops of bowel which may be obscuring the abnormal appendix.

Ultrasound is operator dependent and is variable in sensitivity but highly specific if the appendix is visualized (Taylor, 2014). This may be a useful test, particularly in young patients to avoid the significant radiation penalty of computed tomography. However, the reality in surgical practice is that the appendix is frequently not identified and a negative ultrasound scan is not specific enough to exclude appendicitis. Ultrasound is therefore most useful in scenarios where there is a high probability of an alternative pathology easily detectable on ultrasound such as ovarian pathology in the premenopausal woman or situations where avoidance of radiation is paramount such as in children or in pregnancy. The diagnosis of appendicitis in the younger male remains a clinical diagnosis where ultrasound is rarely helpful and where the radiation exposure from computed tomography is only justifiable if there is significant suspicion of an alternative pathology or an atypical history at presentation. The risks of negative appendicectomy must be weighed against the potential later morbidity associated with radiation exposure.

Computed tomography is more sensitive and specific than ultrasound in the diagnosis of acute appendicitis, with meta-analysis demonstrating pooled sensitivity and specificity for diagnosis in adults at 94% and 94% *vs* 83% and 93% respectively (Doria et al, 2006). Acute appendicitis is demonstrated by appendiceal dilatation of >6 mm with a thickened and enhancing wall, and stranding of the adjacent periappendiceal fat.

An appendicolith may be visible obstructing the appendix orifice. This can be identified on computed tomography as a high-density (calcific) focus which, in conjunction with appendiceal dilatation and an established inflammatory process in the right iliac fossa, is virtually pathognomonic (*Figures 4* and *5*).

Ancillary diagnostic features include ileocolic lymphadenopathy, pericaecal abscess formation or, in the case of perforation, intraperitoneal free gas may be seen.

In pregnancy, where radiation is avoided because of its detrimental effects on both the developing fetus and mother, in exceptional cases magnetic resonance imaging can be performed as a problem-solving tool if clinical

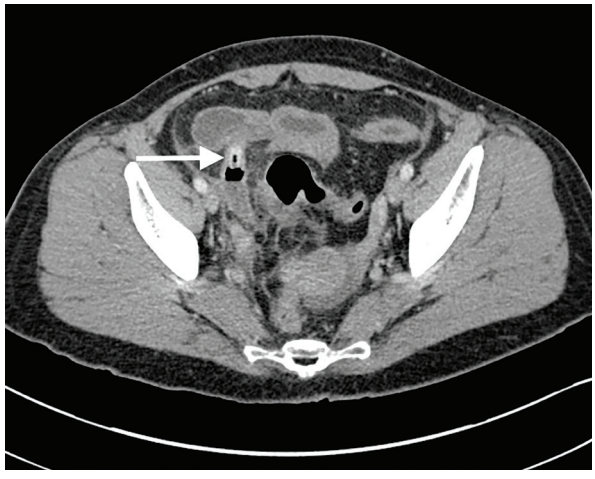


Figure 4. Computed tomography demonstrating acute appendicitis; high density appendicolith (arrowed) associated with appendiceal dilatation and periappendiceal fat stranding.

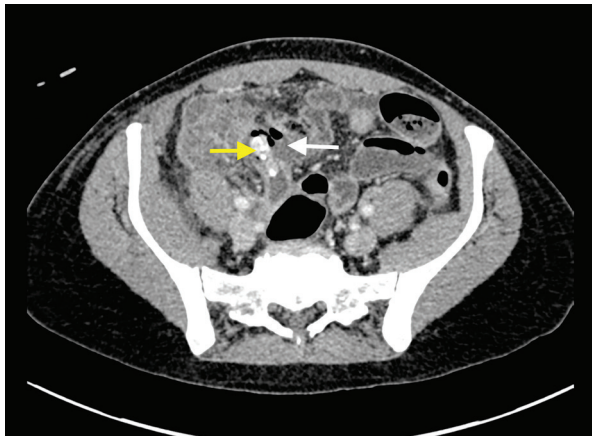


Figure 5. Computed tomography demonstrating acute appendicitis secondary to a high density appendicolith (yellow arrow) associated with perforation of the appendix and adjacent peritoneal free fluid and free gas (white arrow).

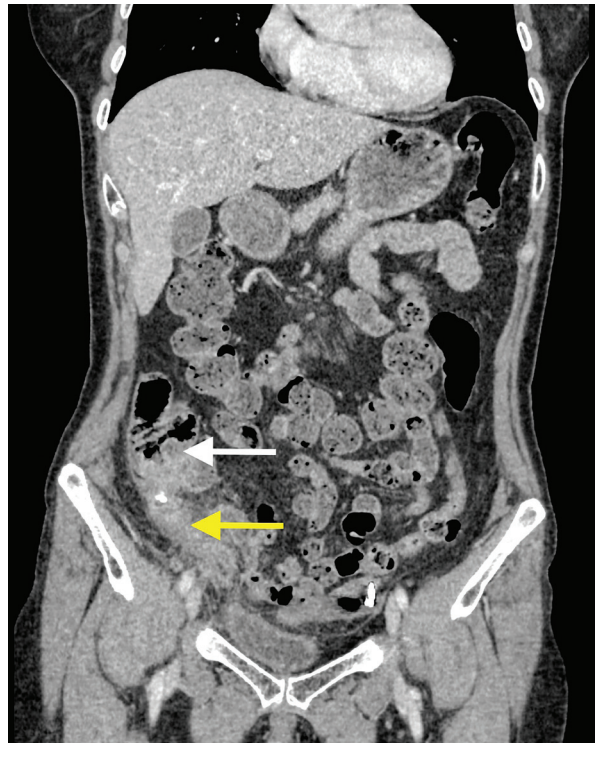
findings and ultrasonography are equivocal. Although magnetic resonance imaging is ideally avoided in pregnancy because of the lack of clinical data to support its safety, particularly in the first trimester, this is can be considered following consultant to consultant discussion and after counselling the patient as to the risks and benefits.

Caecal adenocarcinoma obstructing appendix orifice

The rectosigmoid is the most common site of colorectal carcinoma in the UK, followed by the caecum, transverse colon, ascending colon and decending colon (Hayne et al, 2001). Adenocarcinoma is the most common histological subtype. Right-sided colorectal cancers typically present with non-specific indolent symptoms such as iron deficiency anaemia, weight loss and change in bowel habit. However, a low-lying caecal tumour may obstruct the appendix orifice, presenting as acute appendicitis. There are various morphological subtypes, including circumferential, semi-annular, exophytic, sessile and ulcerated. However, the factor that predisposes to appendicitis is the occlusion of the appendix orifice.

Ultrasound is unreliable in the diagnosis of bowel cancer because of artefact from intraluminal gas. Unprepared computed tomography can similarly be relatively insensitive for the diagnosis of caecal cancer (whereas computed tomography colonography, although contraindicated in cases of suspected appendicitis, has been demonstrated as superior for the diagnosis of colorectal cancer, with sensitivity and specificity similar to that of optical colonoscopy; Halligan et al, 2005). In the context of acute appendicitis, however, computed tomography may show an enhancing mass or eccentric soft tissue thickening within the caecum, which is suggestive of caecal malignancy (*Figure 6*). Currently it is recommended that any colonic cancer should be operated on by a specialist colorectal surgeon. Therefore if a caecal malignancy is suspected preoperatively on imaging, this may allow a more appropriate team to undertake the surgery. If during laparoscopy there is a clear caecal cancer then proceeding to a laparoscopic right hemicolectomy is indicated, but if the diagnosis is equivocal then it is reasonable to convert to open surgery to palpate the caecum and decide between simple appendicectomy *vs* right hemicolectomy as definitive treatment. Careful intraoperative examination of the caecum at laparotomy is vital, which in cases where there is a high index of suspicion for an underlying caecal carcinoma requires conversion to a right or extended right hemicolectomy for definitive treatment.

Figure 6. Coronal computed tomography reconstruction demonstrating acute appendicitis (yellow arrow) secondary to a caecal adenocarcinoma (white arrow) obstructing the appendix orifice. Note the presence of a calcified appendicolith.



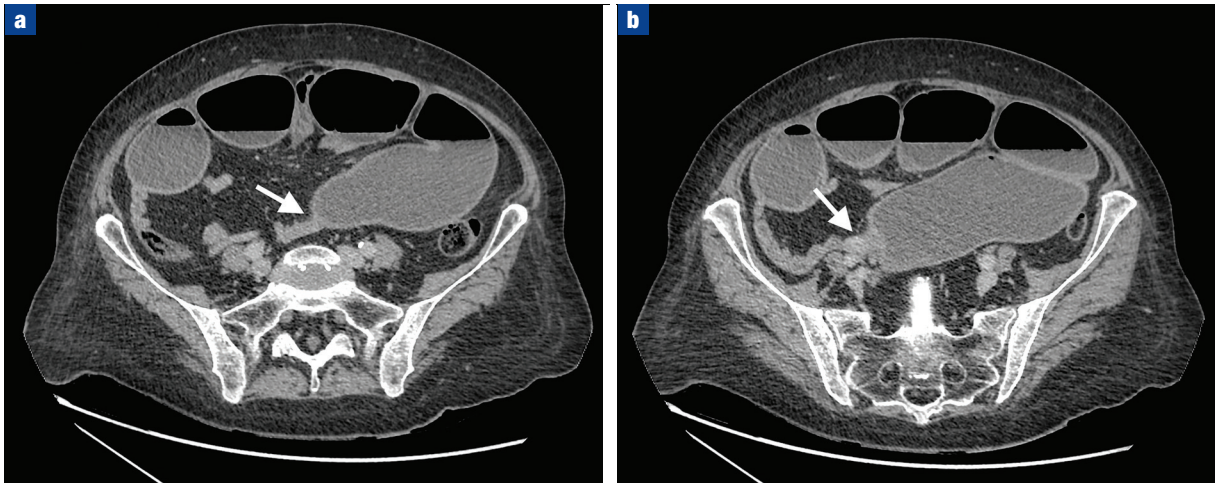


Figure 7. **a** and **b.** Axial computed tomography images demonstrating high grade small bowel obstruction with the appendix draped over the small bowel at the site of transition point (arrowed). Postoperative histology confirmed adenocarcinoma of the appendix with small bowel invasion (T4 tumour).

Appendiceal adenocarcinoma

Primary appendiceal 'colonic-type' adenocarcinoma is relatively uncommon, representing 7% of non-neuroendocrine appendiceal neoplasms in a large case series (Carr et al, 1995). Most patients present with the clinical picture of acute appendicitis and proceed to appendicectomy, and malignancy is identified postoperatively on histological grounds. Mucinous dilatation of the appendix is usually not a feature.

If acute perforation occurs at presentation, this can allow peritoneal seeding of tumour cells, negatively impacting patient outcomes. Definitive management of appendiceal adenocarcinoma requires a right hemicolectomy to ensure oncological clearance.

The radiological features of appendiceal adenocarcinoma are variable, but if visible on computed tomography, it manifests as a soft tissue mass at the appendix. This may be small and confined to the appendix, or if tumour has perforated beyond the wall of the appendix, there may be invasion of local structures. If the appendiceal tumour obstructs the lumen and results in acute appendicitis, the computed tomography appearances will be those of acute appendiceal inflammation and/or a visible soft tissue mass in the appendix downstream of the inflammation.

Rarely, appendiceal adenocarcinoma can present with small bowel obstruction (*Figure 7a, b*) as a result of direct tumour invasion of adjacent small bowel, or from serosal metastatic deposition. In situations where the aetiology of an appendiceal lesion is unclear but the base of the appendix and the point of division is well clear of the lesion it is reasonable to perform an appendicectomy including the mesoappendix. This will allow histological diagnosis and nodal staging without compromising the oncological result by dividing through the tumour.

Mucinous appendiceal neoplasms

A mucocoele describes an appendix that is grossly distended by mucus. This is typically caused by an underlying appendiceal mucin-secreting neoplasm. These lesions lie on a spectrum from low to high grade and have been reclassified on the basis of cellular atypia and morphological features (Carr et al, 2016). In other cases, mucocoele formation may be caused by a benign process such as mucinous hyperplasia or an obstructing mass at the base of the appendix, such as a 'conventional' caecal carcinoma or carcinoid tumours.

On ultrasound or computed tomography, the appendix will appear as a grossly dilated cystic structure. Ultrasound may demonstrate variable internal echogenicity within the mucocoele. In some cases this has a distinctive 'onion skin' appearance which is characteristic of a mucocoele, reflecting layering of internal debris, although this is not always present (Caspi et al, 2004). Computed tomography is the modality of choice for the identification and anatomical delineation of a mucocoele, which presents as a dilated tubular structure that is contiguous with the caecal pole (*Figure 8*), with or without peripheral mural calcification. Similar appearances may be seen on ultrasound (*Figure 9*), although this technique is operator-dependent. Within the mucocoele there may be soft tissue mural thickening, a feature that favours a malignant aetiology.

The appendiceal distension is far greater with a mucocoele than with acute appendicitis. The presence of periappendiceal inflammation is variable, but is often absent in the case of an uncomplicated mucocoele.

Pseudomyxoma peritonei is a condition characterized by disseminated intra-abdominal mucinous deposition, most often secondary to a perforated mucinous appendiceal neoplasm. Other less common causes include colonic, ovarian or pancreatic neoplasms. Hallmark features include mucinous ascites and deposition of mucin within the peritoneum and serosal surfaces. On computed tomography, this manifests as low-density peritoneal nodules or collections, characteristically associated with scalloping of the solid organ contours.

Mucinous appendiceal neoplasms confined to the appendix can be managed with appendicectomy. Once

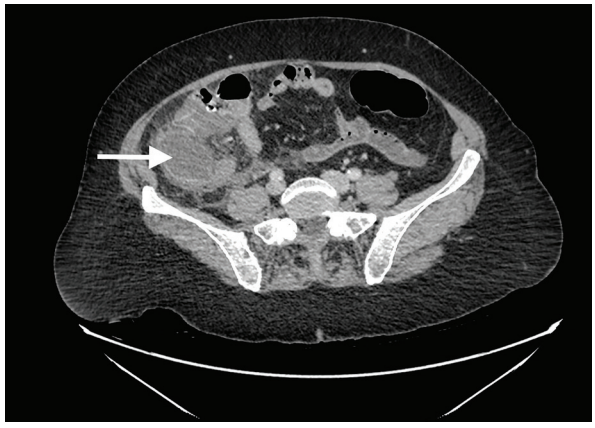


Figure 8. Axial computed tomography demonstrates a dilated, tubular, fluid-filled structure in continuity with the caecal pole, in keeping with an appendix mucocoele.

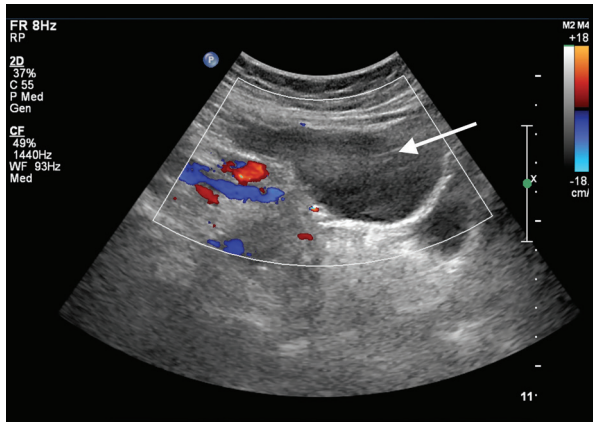


Figure 9. Abdominal ultrasound demonstrates a dilated fluid-filled structure in continuity with the caecal pole, in keeping with an appendix mucocoele.

there is intraperitoneal spread of neoplastic epithelial cells, histological grading of the tumour becomes important, as relatively benign subtypes may benefit from cytoreductive surgery, peritonectomy and hyperthermic intraperitoneal chemotherapy at a specialist centre. This may be inappropriate in higher-grade tumours, with medical management a more rational option (Panarelli and Yantiss, 2000).

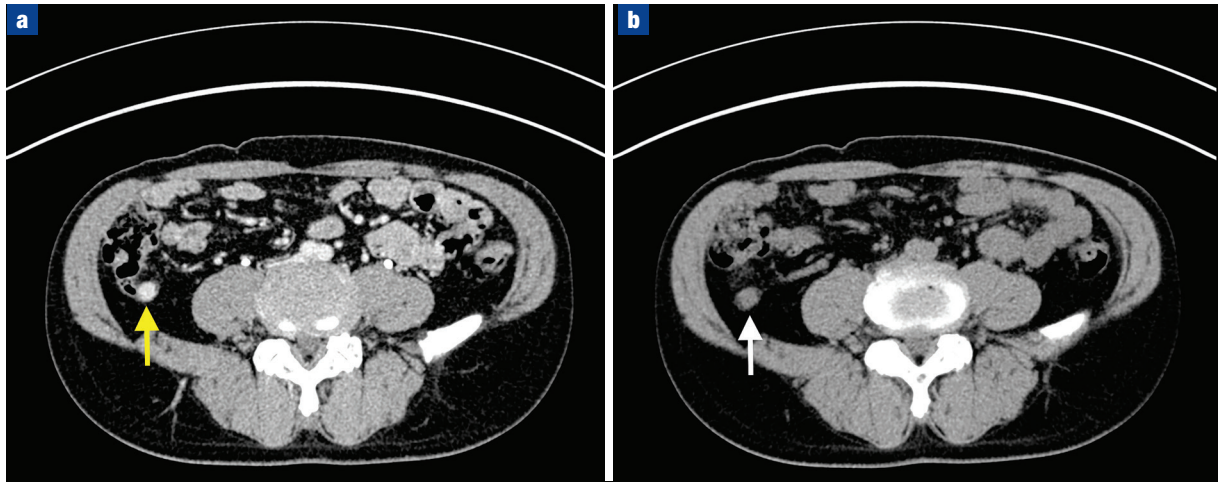
Neuroendocrine tumours of the appendix

Appendiceal neuroendocrine tumours are a relatively rare entity, but represent the most common primary appendiceal neoplasm, and up to 30% of neuroendocrine tumours arise in the appendix (Plöckinger et al, 2008). These tumours are derived from neuroectodermal cells and have the capacity to secrete vasoactive hormones, sometimes giving rise to characteristic clinical syndromes. Pathologically, these tumours are very variable, demonstrating a spectrum from indolent to highly malignant cellular features. Clinically, they are commonly asymptomatic and may be found incidentally, but may also present with non-specific pain. In rare cases they are associated with carcinoid syndrome, where symptoms of flushing, erythema, diarrhoea and wheeze arise from excess circulatory levels of serotonin. Neuroendocrine tumours are typically small in size and confined to the tip of the appendix. However, a subset can obstruct the base of the appendix, giving rise to appendicitis or an associated mucocoele.

Radiologically, diagnosis by computed tomography is infrequent as tumours are typically small. However, an avidly enhancing appendiceal mass may be demonstrated, or diffuse circumferential appendiceal thickening may be present (*Figure 10*).

Somatostatin receptor scintigraphy using indium radiolabelled octreotide selectively targets neuroendocrine tumours and has higher sensitivity than computed tomography. Increased uptake will be demonstrated in the lesion and any associated metastases. Co-registered single-photon emission computed tomography combines functional information with the spatial resolution of computed tomography. Newer techniques with gallium positron emission tomography computed tomography offer superior spatial resolution than conventional single-photon emission computed tomography and are increasingly used for diagnosis (Sahani et al, 2013).

Figure 10. Computed tomography demonstrates **(a)** an enhancing nodule within the appendix (yellow arrow) compared with **(b)** the precontrast scan (white arrow). Histology confirmed the diagnosis of an appendiceal neuroendocrine tumour.



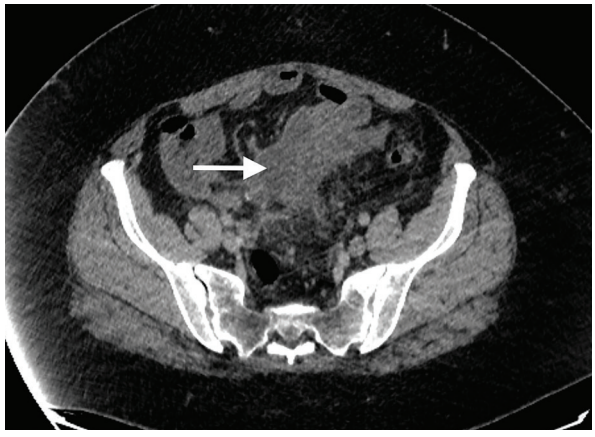


Figure 11. Computed tomography demonstrates a large midline pelvic fluid abscess (arrowed) adjacent to the tip of a dilated, inflamed appendix. Postoperative histology confirmed a fibrotic band across the appendix caused by endometriosis, which resulted in luminal occlusion and subsequent appendicitis with perforation and abscess formation.

However, typically carcinoid tumours are not picked up preoperatively in the context of appendicitis and gallium positron emission tomography computed tomography is used for postoperative staging and follow up.

Current guidance advises simple appendicectomy for tumours smaller than 2 cm with benign features. Right hemicolectomy is indicated in more aggressive tumour subtypes, those larger than 2 cm, and those with adverse features such as local meso-appendiceal invasion, or involved surgical margins. Adverse histological features such as microvascular or peri-neural invasion similarly carry a poorer prognosis. Patients with neuroendocrine tumours should be followed up in a specialist centre with regular monitoring of urinary tumour markers chromogranin A and 5-HIAA and surveillance positron emission tomography computed tomography. Disseminated intraperitoneal metastases can be treated with de-bulking surgery and intraperitoneal chemotherapy. Liver metastases are treated with conventional chemotherapy and/or radiotherapy and ablation (Plöckinger et al, 2008).

Endometriosis

A rare and benign cause of appendicitis in women of childbearing age is obstructing deposits from endometriosis (*Figure 11*). Endometriosis can mimic other pathology on ultrasound, but non-vascular echogenic foci may be visualized. Computed tomography may demonstrate nodular soft tissue foci obstructing the orifice with a characteristic pelvic distribution of disease. Magnetic resonance imaging may be of benefit, but the signal characteristics of endometriosis are highly variable. Direct visualization at laparoscopy is the gold standard for diagnosis. The patient will still require appendicectomy but an intraoperative gynaecology opinion should be sought with photographic evidence taken of the endometriosis to allow ongoing management without need for further diagnostic laparoscopy.

KEY POINTS

- Appendicitis is often a clinical diagnosis, but in cases of diagnostic uncertainty, imaging is a useful tool.
- Computed tomography is more specific and sensitive than ultrasound (which is operator dependent), but ultrasound should be used in younger patients, or in pregnancy, to avoid radiation exposure.
- In patients with an atypical clinical presentation or atypical demography, an underlying malignancy should be considered – if this is confirmed, this can critically alter the definitive surgical management.

Conclusions

Although appendicitis is common the causes can be diverse, ranging from benign to malignant. This broad spectrum is illustrated here, showing the cardinal imaging features and describing the various management strategies. **BJHM**

Conflict of interest: none.

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