SELF ASSESSMENT ANSWERS

An elderly woman with dyspnoea and bronchorrhoea

Q1: What is your diagnosis?
Histological examination of a transbronchial biopsy specimen revealed bronchioloalveolar carcinoma of mucinous type, with extensive vascular invasion.

Q2: What other disorders may show a diffuse alveolar pattern?
Diffuse alveolar radiographic pattern may develop either acutely or as a chronic process. The major causes of both presentations are listed in box 1.

Q3: What are other causes of bronchorrhoea?
Different volumes of daily sputum have been used to define excessive sputum production. Some of its causes are depicted in box 2. Bronchorrhoea is usually accepted as the production of greater than 100 ml/day of sputum.

Discussion
Bronchioloalveolar carcinoma is one of the four recognised subtypes of lung adenocarcinoma. The dramatical increase in the incidence of lung adenocarcinoma in the last decade, being in some series the most frequent of lung adenocarcinoma in the last decade, being in some series the most frequent subtypes have been described: mucinous, non-mucinous, and sclerotic.

Prior pulmonary lesions, some professional exposures, cigarette smoking, and even a viral agent have been proposed as risk factors for developing bronchioloalveolar carcinoma.

Males and females are equally affected. Patients may be asymptomatic in up to half of cases. Clinical symptoms include cough, haemoptysis, chest pain, dyspnoea, and weight loss. Two characteristic features, both present in the case under discussion, are large volume bronchorrhoea and refractory hypoxaemia caused by intrapulmonary shunting.

Radiographic patterns include solitary nodules or masses, localised or diffuse consolidation, and diffuse nodules. In different diagnostic benign and malignant neoplasms (including metastatic disease), lobar pneumonia, congestive heart failure, alveolar haemorrhage, and alveolar proteinosis must be considered. Diagnosis is usually poor, and it has been correlated with the presence or absence of symptoms, tumour extension, and histological type.

The clinical course of this patient was rapidly fatal, and she died on the 11th hospital day after two episodes of massive haemoptysis. Necropsy confirmed the diagnosis and excluded any other primary neoplasm. This was an important finding, as several adenocarcinomas may show pulmonary metastases with histological pictures indistinguishable from primary bronchioloalveolar carcinoma.

Learning points
- The incidence of bronchioloalveolar carcinoma and lung adenocarcinoma have markedly increased in the last decade.
- A non-resolving consolidative pneumonia, despite correct treatment in an adult with normal immunity, must raise the suspicion of bronchioloalveolar carcinoma.
- Diagnosis of primary bronchioloalveolar carcinoma can only be made when other extrathoracic primary adenocarcinomas have been excluded.

Its distinctive pathological feature is growth along the alveolar septae without distortion of pulmonary interstitium. Three histopathological subtypes have been described: mucinous, non-mucinous, and sclerotic.

Box 1: Disorders associated with diffuse alveolar pattern

**Acute**
- Pulmonary oedema.
- Pneumonia.
- Respiratory distress.
- Aspiration.
- Pulmonary haemorrhage.
- Allergic bronchopulmonary aspergillosis.
- Leukaemic infiltrates.

**Chronic**
- Sarcoidosis.
- Tuberculosis.
- Fungal infections.
- Bronchioloalveolar carcinoma.
- Lymphoma.
- Alveolar proteinosis.

Box 2: Causes of excessive sputum production

- Postnasal drip syndrome.
- Asthma.
- Gastroesophageal reflux disease.
- Bronchitis.
- Bronchiectasis.
- Left ventricular failure.
- Diffuse panbronchiolitis.
- Bronchioloalveolar carcinoma.
- Cystic fibrosis.

Final diagnosis
Bronchioloalveolar carcinoma.

Q1: What does the barium enema study (figs 1 and 2; p 341) show?

A small bowel study showed normal stomach and upper small bowel and a somewhat featureless terminal ileum. The caecum and right hemicolon appeared abnormal and a barium enema was suggested. The barium enema (figs 1 and 2) shows classic radiographic features of ileocaecal and colonic tuberculosis confirming a diffusely abnormal terminal ileum with a long stricture affecting the caecum, ascending colon, and proximal portion of the transverse colon with shortening of these bowel segments. The left hemicolon appears normal.

Q2: What is the differential diagnosis and what test should be performed to confirm the diagnosis?

The main differential diagnosis is between ileocolonic Crohn’s disease or tuberculosis. While an intestinal lymphoma or colonic malignancy could produce similar radiological findings, the extent of the colonic involvement in a relatively asymptomatic patient is against these. Other infections—for example, gastrointestinal amoebiasis, acromyocytosis or yersinia, though rare, are possible causes.

The patient was further investigated with a colonoscopy. This revealed ulceration and narrowing at the level of the mid-transverse colon that could not be crossed. Biopsy samples were taken both for standard histological assessment and for tuberculosis culture. Haematoxylin and eosin stains of the biopsy samples showed acutely inflamed granulation tissue but normal underlying colonic mucosa with no evidence of an underlying inflammatory bowel disease, infection or neoplastic process. Ziehl-Neelsen stains were negative for acid-fast bacilli; however, three weeks following the colonoscopy a positive tuberculosis culture was reported. *Mycobacterium tuberculosis* sensitive to isoniazid, rifampcin, and ethambutol was grown.

Q3: What treatment would you initiate?

The treatment of Crohn’s disease and abdominal tuberculosis differ widely. Blind treatment with steroids may lead to deterioration in a patient with tuberculosis. Fortunately, our patient had only mild symptoms allowing the delay of definitive treatment until the results of tuberculosis culture were available. A nine month course of standard antituberculous treatment was started (rifampcin 450 mg daily, isoniazid 300 mg daily, pyrazinamide 1.5 g daily, and pyridoxine 10 mg daily) and was tolerated without any side effects. Her pyrazinamide was stopped after two months.

The inflammatory markers fluctuated over the next nine months but showed a general downward trend. Her weight increased progressively to 46 kg, paralleling her improved exercise tolerance and general clinical condition. A repeat colonoscopy to the caecum was normal with no evidence of residual fibrous scarring. Follow up computed tomography showed thickened bowel loops in the right iliac fossa with some calcification visible in the mesenteric nodes. She remains well 18 months after treatment.

Discussion

Abdominal tuberculosis remains rare, and its incidence over the last decade has remained stable despite variation in reported rates of pulmonary tuberculosis. It is more common in patients with AIDS. As with pulmonary tuberculosis most reported cases in the UK are immigrants. Our patient had never travelled outside the UK but may have been exposed to tuberculosis at the same time as her brother. Another possible source was her neighbours, both recent immigrants, who were found through contact tracing to have active pulmonary tuberculosis.

Her chest radiograph was normal on two occasions. Reports suggest that 20% of patients with abdominal tuberculosis have coexistent pulmonary disease on chest radiography at presentation, but reported rates vary widely (6%–86%). Non-specific symptoms at presentation are not unusual and a high index of suspicion is required to make the diagnosis. In addition to weight loss (66%), abdominal pain (85%), diarrhoea (20%), fever (35%–50%), weakness, nausea, vomiting, melaena, or rectal bleeding may be presenting features. An abdominal mass, usually in the right lower quadrant, is palpable in 25%–50% of patients.

Investigations typically show a normal white cell count. Mild anaemia is common with inflammatory markers characteristically raised. Abdominal ultrasound or computed tomography may confirm an abdominal mass or enlarged lymph nodes but are often unhelpful in distinguishing the underlying cause. Laparoscopy and biopsy can be helpful but are safer if ascites is present, reducing the risk of bowel perforation.

Our case illustrates the value of colonoscopy, biopsy, and culture in establishing the diagnosis. Classical caseating granulomas on routine histology or Ziehl-Neelsen staining may give an immediate answer but may be negative. Fine needle aspiration cytology at colonoscopy may improve the diagnostic yield when nodular lesions are seen. The major disadvantage with tuberculosis culture of biopsy samples is the time taken to get the result. Because of this new “rapid culture” methods have been developed. Approximately 85% of patients will have a positive purified protein derivative or Mantoux test, but a negative result does not exclude the diagnosis. Enzyme linked immunosorbent assay, soluble antigen fluorescent antibody, or polymerase chain reaction based tests have been developed but reduced specificity limits their routine use.

Such extensive colonic involvement is unusual. The ileocaecal region is most commonly involved (75%). Involvement of the transverse colon is less common. The abnormality seen on the initial barium meal investigation remains unexplained. Oesophageal tuberculosis is very uncommon, but usually affects the...
upper half of the oesophagus. It may present with disruption of normal peristalsis secondary to intramural thickening, though thickened mucosa or ulceration is usually visible on endoscopic examination.

Pathologically three gross appearances of intestinal tuberculosis are described: ulcerative, hypertrophic, or ulcerohypertrophic, although there is considerable overlap. Fibrous strictures may develop. Mesenteric lymph nodes are often involved and may calcify. Of the complications, intestinal obstruction is the most frequently encountered (20% of cases). Massive gastrointestinal bleeding is less common. Perforation of the bowel or fistula formation also occur and are associated with a poorer prognosis.

The use of short course chemotherapy for abdominal tuberculosis has not been evaluated in controlled trials but both six and nine month regimens are probably as effective as they are in pulmonary disease. Success rates of 95% have been reported. Occasionally, when investigations have failed to determine the underlying diagnosis, the decision to treat with antituberculous therapy is based on a high index of clinical suspicion alone. This can pose a difficult clinical dilemma, particularly as the main differential diagnosis is Crohn’s disease, which may require treatment with steroids.

Final diagnosis
Abdominal tuberculosis.

Q1: What is the differential diagnosis?
Vertebra plana: differential diagnosis:
- Acute lymphoblastic leukaemia.
- Tuberculosis of the spine.
- Metastasis from neuroblastoma.
- Hodgkin’s lymphoma.
- Langerhan’s cell histiocytosis.

Q2: What further investigations should be performed?
The further investigations that should be performed are a skeletal survey, bone scan, bone marrow aspiration, and biopsy.

In this patient a skeletal survey showed radiographic features suggestive of diffuse marrow or bone infiltration (figs 1A and B and 2). Diagnosis was confirmed by bone marrow aspiration, biopsy of the ileum, periodic acid staining by cytochemistry and detection of cell marker CD10. Bone marrow aspiration revealed a solidly cellular, hypercellular marrow with a high nuclear to cytoplasmic ratio, a scant rim of basophilic cytoplasm without granules and lacy chromatin without conspicuous nucleoli. A biopsy specimen of the peripheral skeletal lesions showed a “streaming artefact” in these patients.

Q3: What is the treatment of this condition?
Musculoskeletal pain does not respond to salicylate treatment, but improves rapidly with chemotherapy. The chemotherapeutic regimen includes induction therapy, consolidation therapy, and reinduction therapy using drugs like prednisolone, L-asparaginase, vincristine, and Adriamycin in combinations.

Discussion
Leukaemia is a haematological disorder that initially may only cause complaints referable to the musculoskeletal system and hence may mimic several orthopaedic conditions when the
chronic childhood diseases. Generalised metabolic dysfunction interfering with the proper osteogenesis of the epiphyseal growth plate results in transverse zones of diminished density.

3. Periosteal bone formation—resulting from the lifting of the periosteum from the centre by the leukaemic infiltrate.

4. Osteolytic lesions—producing a “moth eaten” appearance common in the metaphysis of the long bones and flat bones. These lesions are predisposed to pathological fractures.

5. Osteosclerosis—in the metaphysis of long bones is mostly a late manifestation.

6. Mixed lesions—result from both osteoblastic and osteoclastic activity.

7. Permeative pattern—indicates an aggressive lesion with rapid growth.


In India and other Asian countries tuberculosis of the spine accounts for 50% of skeletal tuberculosis. Lumbar spine involvement is only second in common after lower dorsal spine. A central type of involvement results in vertebral collapse and a vertebral plana-like picture. Usually, the disc space is reduced in association, which is a distinctive feature. Spinal tuberculosis is common both in children and adults and in support with the laboratory investigations may precede as the most likely diagnosis over other local or systemic inflammatory conditions.

As the initial presentation of leukaemia commonly involves the musculoskeletal system, the clinician therefore must include acute leukaemia in the differential diagnosis of any child with unexplained radiographic skeletal pathology.

Final diagnosis

Acute lymphoblastic leukaemia causing osteopenia.

We thank the Dean, KEM Hospital and Seth G S Medical College for granting us permission to use hospital data.

Atopy, proptosis, and nasal polyposis

Q1: What is the diagnosis?

The diagnosis is allergic fungal sinusitis. The diagnosis is based on the clinical features of nasal polyposis and atopy, presence of allergic mucin, characteristic computed tomography features of soft tissue masses interspersed with hyperdense areas filling the sinuses, typical histopathological appearance of allergic mucin, and isolation of Aspergillus flavus on culture.
Q2: What is allergic mucin?
Allergic mucin is the sine qua non of allergic fungal sinusitis. It appears as a cheesy or mucinous, brown, black, or dark green clump of amorphous material interspersed with nasal polypos. It may be seen either on direct nasal examination or at endoscopy. Histological examination of allergic mucin (fig 2; see p 343) reveals eosinophilic or basophilic mucus with an infiltrate of cells which are chiefly eosinophils and many of which are necrotic. The cells are arranged in layers. Fungal hyphae, which are visualised by haematoxylin and eosin or special stains like Gomori-methenamine-silver, may be seen lying loose in the mucus. Charcot-Leyden crystals may also be seen.

Q3: What is the pathophysiology of the disease?
Allergic fungal sinusitis is believed to be the result of Gell and Coombs type I and type III hypersensitivity reaction to a fungal antigen resulting in chronic inflammation and nasal polyps. This is evidenced by the fact that these patients have relatively high eosinophil counts, positive skin allergy tests, and raised total serum IgE levels. Serological evaluation by the radioallergosorbent test or enzyme linked immunosorbent assay also reveals raised IgE and IgG levels to specific fungal antigens like aspergillus or certain dematiaceous fungi in a high proportion of these patients. Histological studies have shown that while there is fungal colonisation, there is no tissue invasion.

Discussion
Allergic fungal sinusitis is a clinical entity which was first described in 1983 by Katzenstein et al, drawing an analogy from allergic bronchopulmonary aspergillosis in which thick mucus plugs, similar to those seen in the sinuses of patients with allergic fungal sinusitis, are seen in the bronchi. Patients with allergic fungal sinusitis classically present with recurrent nasal polyposis, history of having had several nasal surgeries in the past and a strong history of atopy. Unlike patients with simple nasal polyposis, these patients have allergic mucin interspersed with polyps. The presence of eosinophilia, raised IgE levels and positive skin test results to fungal antigens suggest an underlying type I or IgE mediated hypersensitivity in these patients. Similarly, the presence of raised fungal specific IgG antibody levels is indicative of an underlying type III hypersensitivity.

Fungal infections of the sinuses have been classified as mycetoma, non-invasive and invasive fungal sinusitis. Unlike these conditions, allergic fungal sinusitis is an entity which has been classified separately because it is not a true fungal infection. It is believed to be an allergic response to a fungal antigen. Histologically, there is no tissue invasion. This is the case even in patients with clinical and radiological evidence of extensive disease. Patients with allergic fungal sinusitis are not immunodeficient. Fungal culture isolates in these patients include aspergillus species like A flavus or A fumigatus or dematiaceous fungi like Curvularia, Alternaria, or Exserohilum species. These fungi are ubiquitous in nature with a predilection for soil, plants, and damp areas.

Diagnostic criteria for allergic fungal sinusitis are presented in box 1. Some authors include the appearance of the computed tomogram as a diagnostic criterion. Soft tissue densities involving the sinuses with hyperdense areas representing allergic mucin, are the usual features. Allergic mucin shows up as hyperdense areas because of the high content of calcium and magnesium salts within. Occasionally areas of bone erosion or expansion causing extension of disease to adjacent structures like the orbit and anterior and middle cranial fossa may be present. In such cases, differentiation from malignancy is difficult and correlation with clinical and intraoperative findings is imperative.

The mainstay of treatment in allergic fungal sinusitis is surgical excision of polyps and allergic mucin and provision of aeration of the sinuses. This may be achieved by endoscopic sinus surgery or by open procedures like Caldwell-Luc or lateral rhinotomy approaches. Adjunctive steroid treatment given topically as topical steroid; the use of oral steroid and antifungal drugs is recommended by some.

Learning points
- Allergic fungal sinusitis is a disease caused by a type I and type III hypersensitivity reaction to certain fungal antigens.
- There is no histological evidence of tissue invasion by fungus; most authors believe that it is not an infection.
- Allergic mucin interspersed with polyps is the characteristic clinical finding.
- Diagnosis is based on certain definite criteria (box 1).
- Appearance on computed tomography is fairly typical.
- Treatment is by surgical excision with adjunctive topical steroid; the use of oral steroid and antifungal drugs is recommended by some.

Final diagnosis
Allergic fungal sinusitis with proptosis.

Box 1: Diagnostic features of allergic fungal sinusitis
- Recurrent nasal polyposis.
- Presence of allergic mucin.
- Typical histological features of allergic mucin including absence of tissue invasion by fungus.
- Positive fungal culture; aspergillus species and dematiaceous fungi usually isolated.
- Presence of atopy as demonstrated by history, skin tests, or serology.
- Immunocompetent patient.

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Recurrent syncope

Q1: Describe the abnormal features on his 12 lead electrocardiogram

The electrocardiogram (ECG; see p 344) shows marked QT prolongation, U waves, and premature ventricular complexes.

The QT interval is measured from the earliest QRS deflection to the end of the T wave and increases with slower heart rates. It should therefore be corrected for heart rate (QTc) by dividing the measured QT interval by the square root of the RR interval. The maximum QTc in this case is 0.72 seconds with normal values for males and females being 0.46 sec and 0.47 sec respectively.

U waves distort the terminal aspect of the T wave (fig 1) and are thought to represent early after-depolarisations (see below).

Q2: What is the diagnosis and what are the causes of this condition?

The diagnosis is long QT syndrome.

QT prolongation can be divided into acquired and congenital forms.

(1) ACQUIRED

- Bradycardia from any cause including atrioventricular block, hypothyroidism, and hypothermia.
- Ischaemic heart disease.
- Electrolyte abnormalities including hypokalaemia, hypomagnesaemia, and hypocalcaemia.
- Drug therapy (see box 1).
- Starvation/anorexia nervosa.
- Subarachnoid haemorrhage.

(2) CONGENITAL

Two familial forms of QT prolongation are the Romano-Ward (autosomal dominant with normal hearing) and Jervell-Lange-Neilsen (autosomal recessive with deafness) syndromes. A number of genetic mutations have been identified involving the HERG (potassium channel) and SCN50 (sodium channel) genes resulting in abnormal ventricular repolarisation. Individuals have also been identified with genetic mutations that may be insufficient to cause QT prolongation on the ECG but increase the arrhythmogenic susceptibility to drug treatment.

Q3: What classical arrhythmia is associated with this condition?

Torsade de pointes. This is a polymorphic ventricular tachycardia, at rates of 200 to 250 beats/min characterised by a QRS complex that changes in amplitude and has an axis that twists around the isoelectric line. Onset of the arrhythmia is typically preceded by a pause which may be due to sinus arrhythmia, sinus arrest, or more commonly after a premature ventricular complex. The pause may result in early after-depolarisations (U waves) in the next sinus beat, which if of sufficient amplitude, can depolarise the cell and initiate the tachycardia. Episodes are usually non-sustained and may present with palpitations or syncope but there is a risk of sudden death from degeneration into ventricular fibrillation. The relationship between degree of QT prolongation and risk of serious arrhythmia is unpredictable and attempts to assess risk by electrophysiological testing are unrewarding. Women appear to be at increased risk from QT prolongation particularly when caused by drug treatment. Poor prognostic risk factors in patients with congenital QT prolongation include symptoms during infancy, deafness, a history of cardiac

References:


Box 1: Drug associated QT prolongation

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Figure 1: U waves (arrows) resulting in a distorted T wave.
arrest, failure of β-blocker therapy, and a QTc longer than 0.5 sec.\textsuperscript{2}

Q4: How would you treat this man?
The main aim of treatment in long QT syndrome is to identify and correct any reversible cause. This includes correction of electrolyte abnormalities and discontinuing any precipitating drugs.\textsuperscript{3} This man had drug induced QT prolongation having been prescribed chloroquine and astemizole. Both drugs were discontinued and he underwent temporary atrial pacing, at rates of 90–100 beats/min, which can be life saving by reducing the QT interval and preventing an arrhythmia.\textsuperscript{2} Permanent pacing may of course be necessary if there is underlying atrioventricular block. IntraVenous magnesium, while having little effect on the QT interval, is highly effective at suppressing recurrent tachycardia de points, even if the plasma level is normal.\textsuperscript{3} As episodes of tachycardia can be induced by physical and emotional stress sedation should be considered. In the acquired forms of this disorder, once the underlying cause has been treated the QT interval returns to normal and long term treatment is usually not required.

In the case of the congenital long QT syndromes, however, long term treatment with β-blockers is indicated often in conjunction with permanent pacing. An implantable cardioverter defibrillator may be necessary when symptoms recur despite combination therapy and following survival from cardiac arrest.\textsuperscript{2} Screening of relatives is mandatory.

Final diagnosis
Drug induced long QT syndrome.

Q2: What are the guidelines in the investigation of menorrhagia in a women under 40 years?
A history should be taken, abdominal and pelvic examination performed, and a full blood count obtained in all women presenting with a history suggestive of menorrhagia. Tests for thyroid function and bleeding disorders should be performed only if clinically indicated.\textsuperscript{4} If the menorrhagia persists despite evidence based medical therapy then endometrial assessment is indicated.\textsuperscript{4} This should be by transvaginal scan and endometrial biopsy. Hysteroscopy may also be considered.

Q3: What further course of management should be recommended for this patient?
This patient should be referred to the clinical geneticists for advice regarding her potential risk of developing breast and colonic cancers.\textsuperscript{5} Furthermore she should be offered entry into any trial where genes for human non-polyposis colorectal cancer are being studied. Breast and gastrointestinal tract surveillance should be offered.

Discussion
The occurrence of metachronous cancers in an individual is well recognised.\textsuperscript{4} However the occurrence of three different gynaecological primaries in a premenopausal women within three years is a unique clinical occurrence.

This case serves as a salutary reminder that in patients who develop cervical malignancies of the genital tract, the possibility of a new primary carcinoma must be considered in addition to possible recurrence of the original tumour. These patients are at greater risk than the normal population for the development of a new primary carcinoma.\textsuperscript{1}

The incidence of invasive carcinoma of the cervix in women aged 25–34 has increased\textsuperscript{4} and with this the challenge of tailoring surgery to preserving fertility. Burghardt et al., in a series of 16 patients with small volume, stage 1B disease reported no recurrence of disease after five years after treatment with cone biopsy or simple hysterectomy.\textsuperscript{5} More recently, Shepherd et al., described radical trachelectomy with pelvic lymphadenectomy as a surgical option for preserving fertility potential in early stage cervical carcinoma.\textsuperscript{5}

Our patient had early, small volume disease and although technically had stage 1B disease was managed as having stage 1A1 disease. Nevertheless the subsequent histological reports of her uterus, cervix, para-aortic and pelvic lymph nodes after her surgery for her ovarian and endometrial cancers found this

Sequenential occurrence within three years in a premenopausal woman of cervical, ovarian, and endometrial cancers

Q1: What is the management of a 1B squamous cervical carcinoma in a patient who wishes to preserve fertility?
Standard practice for the management of patients with cervical 1B carcinoma is either radical hysterectomy and bilateral pelvic lymphadenopathy for small volume disease (<4 cm diameter) or radiotherapy for large volume disease. The initial step at laparotomy is to assess the pelvic lymph nodes and to send for frozen section any that are thought to be “suspicious”. If the pelvic lymph nodes are shown to be involved with disease, surgery is abandoned and radiotherapy instituted. In patients who wish to preserve their fertility and have small volume stage 1B disease then there is increasing evidence that conservative surgery may be a therapeutic option.\textsuperscript{1} It must be stressed that the literature advocating conservative interventions are small and no randomised controlled trials have been performed. Accepting these caveats and after appropriate counselling a patient may undergo cone biopsy and pelvic lymphadenectomy (either performed via the laparoscope or at open surgery) or radical trachelectomy and pelvic lymphadenectomy.\textsuperscript{2}

management to have been successful in treating her cervical disease. The question arises therefore—is it absolutely necessary to add pelvic lymphadenectomy after cone biopsy for stage IB small volume disease?

In view of the increased predisposition to developing a new malignancy, the initial laparotomy for the ovarian cyst should have been a staging laparotomy despite a normal CA 125 and reassuring scan. Furthermore because of this increased predisposition to a further malignancy, the preferred option would have been referral to a gynaecological oncological centre, following the recommendations of the NHS Executive.

This patient’s personal and family history is strongly suggestive of hereditary non-polyposis colorectal cancer (HNPCC). People from families fulfilling criteria for HNPCC have a 50% risk of being a gene carrier and a 30% sex average life time risk of developing colorectal cancer. In addition they have an excess risk of developing other cancers, namely endometrial (40%), ovarian (10%), and gastric (20%) and other tumours where the risk is lower.

There is class B evidence for implementing biannual colonoscopy as a screening tool to improve survival in these HNPCC families. In addition it would be prudent to perform endoscopy at the same time. Unfortunately, there are morbidity and mortality risks associated with colonoscopy and therefore in an ideal world, gene testing should be employed to identify those carriers of the gene in whom targeting of colonoscopy could be implemented.

Although the gene has been mapped, this test is only available in some centres on the NHS. Families of HNPCC patients must therefore be counselled accordingly regarding the probabilities of being a carrier of the HNPCC gene and the risks and benefits of gastrointestinal tract surveillance.

In this patient’s case ulcerative colitis also predisposes to colorectal cancer. If there had been no personal or family history of bowel pathology the patient would have been at risk of a gastrointestinal tract primary on the basis of her endometrial and ovarian cancer and would have been offered gastrointestinal tract surveillance, although she would have been at less risk than if she had the HNPCC mutation.

In addition to gastrointestinal tract surveillance the patient should also be offered entry into the breast screening programme. Again the exact risk is not known.

Finally, this case highlights the fact that guidelines are precisely that—guidelines. The Royal College of Obstetricians and Gynaecologists in their evidence based clinical guidelines suggest that an endometrial biopsy is not necessary in the initial management of menorrhagia. The Gynaecology Audit Project in Scotland II are more stringent in their recommendations by suggesting an age cut off of 40 years before endometrial sampling should be routinely employed. Although both bodies acknowledge that endometrial evaluation is warranted in a subgroup of women for whom the risk of endometrial cancer is greater than that of the general population, neither body recognises a previous history of genital tract neoplasm as a risk factor. We argue therefore that this is an oversight and that in a woman with a history of a previous gynaecological malignancy, an endometrial biopsy should be performed as part of the initial investigation of menorrhagia regardless of age.

Learning points
- Incidence of invasive carcinoma of the cervix in women of childbearing potential is increasing.
- After conservative surgery for cancer, new symptoms must be regarded with a high index of suspicion as occurring from another possible primary.
- Guidelines are only guidelines and a low threshold for implementing them must be employed in patients with a previous history of carcinoma.
- In patients with a previous history of gynaecological malignancy and presenting with a new symptom referable to the genital tract early referral to the regional gynaecological centre should be employed.
- Referral to clinical geneticists is prudent so that risk regarding other systems can be calculated and appropriate management employed.

An 80 year old woman with intermittent severe vomiting

Q1: What does the chest radiograph show?

The chest radiograph (see p 345) shows a large hiatus hernia extending behind the heart and into both lung fields.

10 Gynaecology Audit Project in Scotland II. Endometrial sampling and D&C feedback report, June 1996. (Project initiated by the Scottish Executive Committee of the RCOG and funded by CRAG. Copies are available from Dr Gillian Penny, Scottish Programme for Clinical Effectiveness in Reproductive Health, Room 64, Aberdeen Maternity Hospital, Foresterhill, Aberdeen.)
Q2: What investigation is shown in fig 2 and what does it demonstrate? How does this relate to the presenting complaint?

Figure 2 (see p 345) is a single film from a barium meal series. The film demonstrates a partial rolling volvulus of the stomach. This is typically an intermittent phenomenon and when present results in profuse vomiting especially after eating.

Q3: How else can this condition present?

Small hiatus hernia rarely cause symptoms other than reflux which can usually be controlled medically, but giant hiatal hernias, where the majority of the stomach is intrathoracic as shown here, can present in a number of ways, including:

- Severe reflux, retching, postprandial pain, bloating, and dysphagia due to mechanical pressure from the herniated stomach.
- Haematemesis and iron deficiency anaemia from a “riding ulcer” formed by mechanical ulceration and mucosal ischaemia as the stomach passes through the diaphragm.
- Dyspnoea and aspiration pneumonia due to the loss of lung volume and high frequency of reflux with aspiration.
- Severe epigastric or retrosternal pain with vomiting and fever are features of hernia strangulation.

Q4: How should this woman be managed?

Management of this condition is predominantly surgical. Until recently the decision to operate has been controversial, as patients are usually elderly and therefore the operative risks are high. However, the condition responds poorly to conservative medical therapy and recent improvements in laparoscopic surgery techniques have led to an increase in the number of surgical procedures performed. This woman underwent laparoscopic repair of her hernia with a successful outcome.

Discussion

Hiatal hernias occur commonly with some prevalence estimates suggesting that 15% of the population may be affected. Most hernias are small and are either asymptomatic or associated solely with reflux. However, in a small proportion of hernias the diaphragmatic defect is large enough to allow the majority of the stomach to enter the thoracic cavity forming a “giant hiatus hernia” or intrathoracic stomach. Hiatal hernias are classified according to their mechanism of development into sliding, paraoesophageal, and mixed. Approximately 85% of hiatal hernias are of the sliding type with simple upward migration of the gastrooesophageal junction into the mediastinum. Giant hiatal hernias have traditionally been thought to be of the paraoesophageal type, where part of the stomach passes through a defect in the diaphragm adjacent to the oesophagus. However recent evidence suggests that most hernias, regardless of size, originate as the sliding type. It is postulated that a “giant hiatal hernia” forms when an existing sliding hernia exerts pressure on tissue around the diaphragm resulting in weakness, which ultimately allows the stomach to pass into the thorax alongside the original sliding hernia, thus forming a mixed hernia.

Giant hiatal hernias occur almost exclusively in the elderly and are associated with a number of presentations including postprandial chest pain, symptomatic reflux, dysphagia, vomiting, haematemesis, iron deficient anaemia, dyspnoea caused by lung displacement, and aspiration pneumonia. Strangulation may occur following gastric volvulus and is suggested by severe chest and epigastric pain associated with persistent vomiting. The rate of occurrence of strangulation is controversial but an early series showed six cases in 21 patients with giant hiatal hernias treated conservatively. Physical signs are rarely helpful in making the diagnosis, although bowel sounds may be heard high in the chest and basal breath sounds can be reduced due to upward displacement of the lungs. A chest radiograph may show the stomach as an extramediastinal shadow or there may be an air fluid level behind the heart. Diagnosis is usually confirmed by barium swallow or with fibreoptic endoscopy.

Surgery is thought to be the best management option, as medical therapy does not alter the risk of strangulation or resolve the mechanical displacement of the stomach that accounts for many of the symptoms. Despite these benefits surgery had been controversial as many patients were elderly, but the introduction of laparoscopy has revolutionised the treatment of giant hiatal hernias and has resulted in an increased number of procedures being performed.

Final diagnosis

Giant intrathoracic hiatus hernia.

Pleuropericardial effusion in a 50 year old woman

Q1: What are the common causes of pleuropericardial effusion?

The combination of fever and pleuropericardial effusion is an unusual presenting feature and raises the possibility of infectious, neoplastic and connective tissue disorders. The most frequent causes are listed in table 1.

Q2: What further investigations are necessary in this patient’s case?

Investigations should be directed at determining the cause and will initially involve haematological tests including: full blood count, urea
and electrolytes, liver and thyroid function, inflammatory markers (ESR or C reactive protein), antinuclear antibody (with DNA and extractable nuclear antigen screen if positive), antineutrophil cytoplasmic antibody (ANCA), rheumatoid factor, and serology for viruses and other infective causes. Analysis of the pericardial and/or pleural fluid will nearly always be necessary and should include culture for bacteria and mycobacteria, protein and glucose concentrations, differential cell count, and cytology. Pleural or pericardial biopsy might be indicated if malignancy or tuberculosis is suspected. Specific tumour markers might be helpful in detecting occult malignancy. In this patient’s case thyroid function and other liver function tests were normal, rheumatoid factor, antinuclear factor, and ANCA were negative and serology did not suggest recent bacterial or viral infection by any of the common respiratory pathogens. Cytological and microbiological analysis of the pericardial and pleural fluid did not show any evidence of infection or malignancy. The pleural fluid contained small lymphocytes and neutrophils with total protein 41 g/l. Abdominal ultrasound was used to exclude ovarian carcinoma and other malignancies.

**Q3: The patient’s symptoms and radiology returned to normal after treatment with aspirin 3.6 g daily. What is the likely diagnosis?**

Pleuropericardial effusion in the context of a history of joint symptoms together with fever and negative investigations for connective tissue disorders, malignancy, and infection suggested a diagnosis of adult onset Still’s disease (AOSD). This is a diagnosis of exclusion and in clinical practice care should be taken to continue to look for signs of the more common causes such as rheumatoid arthritis or systemic lupus erythematosus.

**Outcome**

Once AOSD was suspected the patient was started on 3.6 g of aspirin daily in divided doses. Within three days systemic symptoms and pyrexia were beginning to settle and she was discharged. At review three weeks later her cough had disappeared, joint pains had settled, and chest radiography showed partial resolution of the effusions. Eight weeks later the effusions were no longer seen, ESR was 13 mm/hour, and haemoglobin 133 g/l. She remained well for five months when she experienced aching and swelling of both wrists despite continued aspirin and was started on hydroxychloroquine 200 mg twice daily. Reassessment one year after diagnosis showed no serological or clinical evidence of an evolving connective tissue disease, supporting the diagnosis of AOSD.

**Discussion**

AOSD is a rare disorder typically affecting young adults between the ages of 16 and 35 with equal sex distribution. The diagnosis rests on the combination of typical clinical and laboratory findings and diagnostic criteria have been developed by Cush (table 2). Three features (fever, rash, and arthralgia) are common at presentation. A daily spiking fever of 39°C or more is seen in 97% of cases. Eighty eight per cent of cases have a characteristic rash, the so-called “Still’s” rash, which is pink, macular or maculopapular, and evanescent. It usually occurs on the trunk and proximal extremities and may coincide with a fever spike. Arthralgia is universal and most develop a predominantly distal polyarthritis. Pharyngitis, splenomegaly, lymphadenopathy, cardiopulmonary involvement, and hepatomegaly are sometimes seen. Not all the eventual symptoms and signs may be apparent at presentation and the condition can evolve over a period of weeks or months.

The consistent laboratory findings are anaemia, high ESR, leucocytosis, and deranged liver function tests. A negative rheumatoid factor and antinuclear antibody are required for the diagnosis to be made. Infection, malignancy, and other connective tissue diseases may give a similar clinical picture and investigations should be directed at excluding these as possible causes. Additionally when there are any atypical features, such as the age of this patient, it is essential to review the diagnosis after some months to rule out evolving connective tissue disorders.

Pulmonary involvement in AOSD is reported in the largest series to occur in 20%–30% of cases. Pleuritis leading to pleurisy and/or pleural effusions is the commonest pulmonary manifestation. Effusions are usually bilateral and the pleural fluid is an exudate with increased numbers of inflammatory cells particularly neutrophils. Pneumonitis occurs in about 10% of cases giving rise to chest radiograph opacities. Pulmonary function tests generally show a mild restrictive picture and gas transfer may be reduced. The commonest cardiac manifestation of AOSD is pericarditis and pericardial effusion, seen in 26%–28% of cases and usually occurs with pleural effusion.

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**Table 1 Causes of pleuropericardial effusion**

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Viruses (influenza, cytomegalovirus, coxsackie), bacteria (klebsiella, legionella, listeria) mycobacteria, fungi (actinomycosis)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Carcinoma, lymphoma, leukaemia, Kaposi’s sarcoma</td>
</tr>
<tr>
<td>Connective tissue disorders (CTD)</td>
<td>Rheumatoid arthritis, systemic lupus erythematosus, mixed CTD and other systemic vasculitides, adult onset Still’s disease</td>
</tr>
<tr>
<td>Cardiac causes</td>
<td>Post-cardiac injury syndrome, constrictive pericarditis</td>
</tr>
<tr>
<td>Drugs</td>
<td>Methotrexate, mesalazine, tretinoin, tryptophan</td>
</tr>
<tr>
<td>Metabolic and endocrine</td>
<td>Uraemia, hypothyroidism, hypoparathyroidism</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2 Criteria for the diagnosis of adult onset Still’s disease**

<table>
<thead>
<tr>
<th>Requirement</th>
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<tr>
<td>The diagnosis requires the presence all of the following:</td>
</tr>
<tr>
<td>Fever &gt;39°C</td>
</tr>
<tr>
<td>Arthralgia or arthritis</td>
</tr>
<tr>
<td>Rheumatoid factor &lt;1:80</td>
</tr>
<tr>
<td>Antinuclear antibody &lt;1:100</td>
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</table>

In addition to any two of the following:

- White cell count >15 000 cells/ml
- Still’s rash
- Pleuritis or pericarditis
- Hepatomegaly or splenomegaly or generalised lymphadenopathy
Tamponade occurs in 1%–2% of cases. Rarer cardiac findings are myocarditis (5%) and endocarditis.

The treatment of choice is a salicylate, usually aspirin, in high dose and this may be combined with another non-steroidal anti-inflammatory drug (NSAID) if there is no response to a single agent. Altogether 20%–25% of patients respond to NSAIDs alone. Systemic corticosteroids can be used if symptoms fail to improve with these measures and prompt remission is typical. Disease modifying antirheumatic drugs may be required particularly if joint symptoms persist as was the case in this instance and intramuscular gold, penicillamine, sulfasalazine, and hydroxychloroquine have been used. Methotrexate may be useful if systemic features are present. The majority of patients can expect prolonged or permanent remission, however, intermittent relapses or chronic disease course does occur in 30%–50% of cases. During follow up it is necessary to check rheumatoid factor and antinuclear antibodies regularly to ensure that the presenting illness is not an early presentation of another connective tissue disorder.

This case fulfils the diagnostic criteria for AOSD except for the finding that the leucocytosis was slightly below that stipulated by Cush. As alternative diagnoses were sought thoroughly but not found and the patient responded completely to NSAIDs we feel this is the likely diagnosis. She was unusual in her late age of presentation and this increased the importance of excluding malignancy. The absence of a Still’s rash and the relatively minor articular involvement are associated with a better prognosis. Response to NSAID treatment is also associated with a favourable outcome. Awareness of the condition is important when investigating patients with pleural and pericardial effusions particularly when these occur together.

**Final diagnosis**

Pleuropericardial effusion caused by adult onset Still’s disease.