A complicated case of von Hippel-Lindau disease

Q1: What family history should be explored in a 17 year old girl with multiple cerebellar haemangioblastomas and why?
The development of haemangioblastoma within the central nervous system is a common first manifestation of von Hippel-Lindau disease, which is inherited in an autosomal dominant fashion. A careful family history would be expected to reveal similar features of the condition within first/second degree relatives, unless the presenting case represents a sporadic mutation. In this case, there was no such history and subsequent genetic analysis confirmed the diagnosis by revealing a 796C→T nonsense mutation in exon 3 of the von Hippel-Lindau gene.

Q2: What is the nature of the current problem and unifying diagnosis?
Computed tomography reveals a 4 cm round solid right adrenal mass. The MIBG scan shows a focal area of high uptake within the same region. These appearances are consistent with a right adrenal pheochromocytoma, a recognised complication of von Hippel-Lindau disease.

Q3: What other complications occur in this disease?
Various other tumours are associated with von Hippel-Lindau disease. These are often multiple, and present at an earlier age than the sporadic variety. Retinal and cerebellar haemangioblastomas are the most frequently observed complications, seen in 50%. These are benign tumours, which cause symptoms via the mass effect. Retinal lesions cause disturbance of vision and can lead to blindness if left untreated. This complication has been observed to be the first manifestation of the condition in 43% of affected patients. Renal cell carcinoma occurs in 28% of patients, and is the most common cause of death. Phaeochromocytomas occur in 7%–19% of patients. Although most are benign and located within the adrenal gland, some tumours can be extra-adrenal and malignant.

Q4: What is the significance of thyroid cancer in the mother?
Multiple endocrine tumours within first degree relatives occur in other inherited conditions. Phaeochromocytoma and medullary carcinoma of the thyroid gland may be seen together as part of the multiple endocrine neoplasia (MEN) type IIa (Sipple’s) syndrome. Although theoretically, any histological subtype of thyroidal carcinoma can undergo anaplastic degeneration, there is no genetic association per se between phaeochromocytoma and anaplastic carcinoma of the thyroid. In addition, other manifestations of the MEN syndrome would certainly have been expected in the mother by her age.

Final diagnosis
Right adrenal pheochromocytoma occurring in a patient with known von Hippel-Lindau disease.

An unusual cause of paraplegia

Q1: What differential clinical diagnoses would you consider?
The differential diagnoses include:
- Inflammatory; vasculitis/granulomatosis.
- Infective—for example, tuberculosis of the spinal cord, tertiary syphilis.
- Vascular—for example, anterior spinal artery thrombosis, embolic phenomena (for example, subacute infective endocarditis), sagittal sinus thrombosis.
- Paraneoplastic.

Q2: What do the spinal MRI scans show (see p 472)?
The scans show swelling of the spinal cord from the middle thoracic region to the conus medullaris. The margin of the spinal cord is unclear with intramedullary increased signal intensity and the spinal canal seems to be occupied mostly by the swollen cord.

Q3: What was the first treatment given which was followed by paraplegia?
The patient was started on intravenous methylprednisolone infusion (1 g daily) for presumed inflammatory myelitis/vasculitis. On the third day and after two infusions, he lost bladder sensation and knee jerks, and became paraplegic. The steroids were stopped. In our experience this is the second patient with a similar presentation who developed paraplegia after intravenous steroids.

Q4: What is the pathological abnormality suggested by the spinal angiogram (see p 472)?
The spinal angiogram shows an arteriovenous fistula fed from the left T5 intercostal artery.

Q5: What specific treatment did the patient receive?
The vessel was catheterised and its feeder (the fistula) was blocked with coils and glue.
Discussion
Spinal arteriovenous malformations (AVMs) are rare. The majority are radiculomeningeal, also known as spinal dural arteriovenous fistulas. The condition is thought to be caused by venous hypertensive congestion of the spinal cord caused by dysfunction of the “draining” nearby dural sinus.

There are no pathognomonic clinical features and the diagnosis may be difficult unless there is a high degree of clinical suspicion. Even in younger patients treatable causes of paraplegia are often diagnosed late with tragic results.

In a review of 55 cases, AVMs were more common in males (7:1) with an average age of presentation at 57 years. The most common symptom was weakness of the legs (95%), accompanying impairment of bladder function (89%), and impairment of bowel control (85%). Most patients had a combination of motor, sensory, and sphincter disturbance. The clinical course was progressive in most patients (78%) and acute in onset in 11% of patients.

The duration of symptoms was less than three years in 66% of patients and less than one year in 10% of patients.

Our patient did not have signs of infection or malignancy, but he did have radiological features of ischaemic/necrotic spinal cord which would explain the rising inflammatory markers as his symptoms progressed.

The development of selective spinal angiography in the early 1960s has enabled better evaluation and classification of AVMs. An analysis of 240 spinal angiograms in 132 patients revealed 97 AVMs that included 66 spinal dural AVFs. The nidus of the fistula was located between T6 and T12 in 61%, in the sacrum in 9%, and intracranially in 8% of cases.

The advantages of MRI in demonstrating intramedullary malformation are multiplanar imaging, high soft tissue contrast, and absence of ionising radiation. Successful management depends on early suspicion of the diagnosis and confirmation of the disorder and a clear understanding of the lesion’s anatomical location as early treatment may only slow the progression of the disease rather than reversing symptoms or acquired deficits.

Treatments of AVMs include surgery, embolisation, or both. Endovascular treatment is less invasive, causes less morbidity, and may ensure earlier recovery. If embolisation has failed, surgery can still be an option.

Morgan and Marsh described recanalisation in 11 of 18 embolisation treatments in 14 patients using polyvinyl alcohol with recurrence of symptoms. In a recent report of 18 patients Marey et al recommend that N-butylcyanoacrylate embolisation be the initial treatment of choice for arteriovenous fistulas with venous drainage. Patients should be followed up closely with periodic clinical and radiological assessments. MRI and spinal angiography are essential to achieve the best clinical benefit and possible cure.

Learning points
- Spinal AVMs are rare disorders that should be added to the list of causes of progressive leg weakness in middle aged and elderly patients.
- It is associated with considerable difficulty in diagnosis which can lead to treatment delay in most patients.
- Successful treatment requires early diagnosis and the correct understanding of the anatomy of the lesion and its angioarchitecture and the limitations of both surgery and endovascular embolisation.

Final diagnosis
Spinal dural arteriovenous fistula.


Palpable breast mass in a lactating woman

Q1: What is the differential diagnosis of a solid mass in a pregnant or lactating woman?

Breast masses are encountered frequently during pregnancy. As in non-pregnant women of childbearing age, most breast masses encountered during pregnancy and lactation are benign. The main differential considerations for a palpable solid breast mass in the pregnant or lactating female are listed in box 1. Of these, lactating adenoma and fibroadenoma are the two most prevalent. The incidence of breast cancer in this group of patients is low and the likelihood of diagnosing cancer in pregnancy or lactation is similar to that in the non-pregnant population. About 3% of breast cancers are diagnosed during pregnancy.

Q2: What further work-up is needed to confirm the diagnosis in this case?

Due to the hypertrophic changes occurring in the breast during pregnancy and lactation, there is a dramatic increase in its radiographic density, which severely decreases the sensitivity of mammography for the diagnosis of breast masses. Ultrasound is the preferred initial study for evaluating a palpable mass in this group of patients. This determines the solid or cystic nature of the mass. However, once a solid mass is diagnosed, ultrasound cannot be relied
Main differential considerations for a palpable solid breast mass in the pregnant or lactating female

- Lactating adenoma.
- Fibroadenoma.
- Tubular adenoma.
- Lobular hyperplasia (normal physiological event in pregnancy).
- Breast cancer.
- Focal mastitis.
- Phyllodes tumour.

Upon to distinguish benign from malignant lesion and tissue sampling is usually warranted to avoid delay in diagnosis of breast cancer. Fine needle aspiration cytology has been associated with some false positive and false negative results, particularly in the setting of lactating adenomas.\(^1\) Ultrasound guided core biopsy is therefore often necessary for a definitive diagnosis.

Q3: What is the most likely diagnosis of this patient’s palpable breast mass?

The breast mass in our patient is most likely a lactating adenoma as this is the most commonly encountered solid mass in a pregnant or lactating patient, accounting for as many as 70% of all biopsied lesions in this population.\(^1\) The clinical and sonographic features, although non-specific, are certainly compatible with this benign entity. Ultrasound guided core biopsy of the mass confirmed the diagnosis of lactating adenoma with some focal areas of necrosis.

Outcome

Given the benign nature of the mass, a short term follow up was chosen. The patient continued to breast feed as usual. At follow up examination after three months, the mass was no longer palpable. A repeat ultrasound at this time confirmed complete resolution of the previously seen mass.

Discussion

Also called “lactational adenoma” or “breast tumour of pregnancy”, lactating adenoma is a benign stromal tumour that occurs only in association with gestation and is typically seen from the third trimester through the period of lactation. Clinically, it is generally a firm, mobile and non-tender mass, that usually regresses spontaneously after the cessation of breast feeding. Bromocriptine is occasionally used to induce shrinkage of these tumours.\(^1\) Surgical excision of a persistent mass is generally deferred until the resolution of lactational changes. There is no convincing evidence for an association with oral contraceptives or an increased risk of breast cancer.\(^1\)

The ultrasound features, although favouring a benign mass, are quite non-specific and may mimic malignancy. Characteristically, lactating adenoma is a solid mass between 1 and 4 cm in diameter, ovoid or macrolobulated, with well defined margins and its long axis parallel to the chest wall.\(^1\) It is typically homogeneous and hypoechogenic with posterior acoustic enhancement. Hyperechoic fibrous bands coursing through the lesion and a prominent central duct have been described.\(^2\) Occasionally, however, indistinct or irregular margins, heterogeneous echotexture, and posterior acoustic shadowing may be present, making the distinction from a malignant mass more difficult.\(^3\) Core biopsy is often needed to confirm the diagnosis. Histopathologically, the mass lacks a true capsule and is composed of proliferating distended tubules and secretory lobules lined by uniform lobular cells with a granular and vacuolated cytoplasm, surrounded by a basement membrane and oedematous stroma.\(^1,4\) These gestational changes are characteristically out of phase with the actual stage of pregnancy. There may be frequent mitotic figures, but there is no cellular atypia. Differentiation from lactational changes in a pre-existing fibroadenoma is possible since these changes in a fibroadenoma tend to be focal and the underlying characteristic architecture of the rest of the tumour is preserved.\(^4\) Lactating adenomas also have a distinctive immunohistochemical phenotype.\(^1\) Necrosis and haemorrhage are not prominent features of lactating adenomas, with only 5% demonstrating histological evidence of infarction.\(^1\) Infarction may result in a rapidly enlarging mass that may reach considerable size.\(^5\)

Final diagnosis

Lactating adenoma of the breast.

A patient with severe hyperphosphataemia

Q1: What is the cause of the hyperphosphataemia?

The disproportionate hyperphosphataemia in this context is related to a phosphorus-containing laxative that is prescribed to patients with chronic renal failure. An acute rise in plasma phosphate is characteristically accompanied by hypocalcaemia, which accounts for most of the symptomatology. The patient had been given an oral laxative preparation containing 2.4 g monobasic sodium phosphate and 0.9 g dibasic sodium phosphate per ml. Fleet Phospho-Soda contains 4.25 mmol/l inorganic phosphate per ml. In fact, ingestion of 20 ml over three to six hours can give rise to substantial hyperphosphataemia, which may be aggravated by extracellular fluid volume contraction (due to diarrhoea) and renal insufficiency (due to decreased renal perfusion).

Other possibilities including rhabdomyolysis and spurious (pseudo) hyperphosphataemia...
from a haemolysed specimen should also be excluded (see box).

**Classical examples of hyperphosphataemia**

*Increased exogenous load*
- Phosphate-containing enema.
- Vitamin D intoxication.

*Increased endogenous load*
- Rhabdomyolysis.
- Tumour lysis syndrome.
- Reduced urinary excretion
- Renal failure.
- Pseudohyperphosphataemia
- Haemolysis in vitro.
- Multiple myeloma.

**Q2: What action would you take?**
Acute hyperphosphataemia secondary to a phosphorus-rich laxative or enema is managed according to our understanding of serum phosphate regulation and the concept of calcium × phosphate concentration product.

The most effective way to correct hyperphosphataemia is reduction of the intestinal load or absorption by limiting phosphate intake as well as ingestion of phosphate-binding salts of aluminium, magnesium, or calcium. The magnesium concentration should be checked, and if low, corrected. In the presence of both hyperphosphataemia and hypocalcaemia, calcium supplementation should be handled cautiously in parallel with phosphate binders and, preferably delayed until the serum phosphate has fallen below 2.0 mmol/l to avoid soft tissue calcium phosphate precipitation. The calcium × phosphate concentration product of 5.6 in SI units has been widely quoted as the threshold above which metastatic calcification occurs theoretically. The corresponding calcium × phosphate concentration product in our patient was 8.2.

Our patient was managed in this way and her electrolytes were under control six days after colonoscopy (table 1; see p 473). Her serum creatinine concentration further improved to 436 µmol/l one month later, while her calcium was maintained at 2.52 mmol/l.

**Q3: How should this be avoided?**
Patients with moderate to severe renal insufficiency should preferably avoid use of laxatives with a high phosphorus content. If they are used, careful monitoring is warranted.

**Discussion**

Hyperphosphataemia is generally a reflection of reduced renal function and the occurrence is dependent on the balance between renal excretory capacity and exogenous phosphate loads. Tumour lysis syndrome classically illustrates an acute overwhelming phosphate load exceeding the usual renal excretion; less frequently, use of oral and rectal bowel preparations containing sodium phosphate is associated with serious hyperphosphataemia. The risk of prescribing sodium phosphate for cathartic purpose in the presence of renal impairment has been recognised and a mortality rate of up to 33% reported.

This life threatening phenomenon has been described in adults ranging from 37 to 88 years of age.

An increase in the serum phosphate concentration stimulates the secretion of parathyroid hormone, which will inhibit proximal tubular sodium-phosphate cotransporter. Urinary phosphate excretion tends to increase as a result of an increased filtered load of phosphorus and decreased tubular reabsorption. However, in the presence of diminishing glomerular filtration or functioning nephrons, the phosphaturic effect is blunted and hence acute hyperphosphataemia ensues. In fact, phosphate reabsorption is maximally suppressed once the glomerular filtration rate falls below 20–25 ml/min.

Risk factors of acute hyperphosphataemia complicating exogenous inorganic phosphate administration for bowel preparation have been elucidated in various case reports. The most commonly quoted ones include renal impairment, advanced age, and impaired intestinal motility.

It is noteworthy that our patient was managed without dialysis, as has been reported before. Choice of treatment has been thoroughly reviewed by Sutters et al. Ways to tackle a raised phosphate concentration include increased renal excretion (diuresis and dopamine if applicable), redistribution (insulin/dextrose and correction of acidosis), and deposition into bone (administering calcium). Decreased absorption (oral phosphate binders) and direct removal (by haemodialysis) should also be underscored. Haemodialysis has been thought of as one of the most effective short term treatments of hyperphosphataemia, particularly in the context of renal dysfunction. On the other hand, our case illustrates the option of oral phosphate binders. It seems prudent to administer phosphate binders against a background of acute hyperphosphataemia.

**Final diagnosis**

Acute hyperphosphataemia secondary to a phosphate-containing oral laxative in chronic renal failure.

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Abnormal behaviour in a man with massive, generalised, peripheral lymphadenopathy

Q1: What are the diagnoses?
The diagnoses are disseminated cryptococcosis with meningoencephalitis and massive generalised lymphadenopathy, intestinal cryptococcosis, and oropharyngial candidiasis in advanced HIV disease.

Q2: What is unusual and atypical in the case illustrated?
The following features are unusual for classical meningitis:
- Absence of positive indicators of meningitis like neck rigidity.
- Normal concentrations of glucose and protein and absence of pleocytosis in the CSF. Thus absence of neck stiffness and absent CSF pleocytosis does not necessarily rule out fungal meningitis; this underscores the need for high clinical suspicion in the immunocompromised host.
- Massive peripheral lymphadenopathy is rare in cryptococcosis.
- The absence of respiratory involvement in disseminated cryptococcosis, despite the lung being the portal of entry for cryptococcus, is an unusual feature.
- FNAC of the lymph node has proved in this case to be a very simple, reliable, and rapidly useful diagnostic test in evaluating cryptococcal lymphadenopathy.

Discussion

_Cryptococcus neoformans_ is by far the most common, potentially fatal fungal pathogen in patients with HIV infection. It accounts for approximately 5%–10% of all opportunistic infections in patients with HIV disease. The lung, brain, and meninges are the most frequently involved sites in systemic cryptococcosis. Subacute meningitis with or without encephalitis is the most common clinical form followed in frequency by pulmonary infections and disseminated infection. 

Cryptococcal meningitis in the immunocompromised host often presents with subacute, non-specific symptoms referable to the central nervous system such as headache, nausea, dizziness, irritability, somnolence, clumsiness, confusion, and impaired memory and judgment.

Positive meningitis indicators may not be present, as in our patient, who had no meningeal signs. This underscores the significance of CSF analysis when fever and constitutional symptoms alone are reported by patients with advanced HIV disease especially when the serum levels of cryptococcal antigen (CRAG; not done on our patient) titres are raised. It is well known that the latex agglutination test for CSF-CRAG is a rapid, reliable, and sensitive confirmatory diagnostic test for cryptococcal meningitis in patients with normal CSF findings (our patient had normal values for glucose and protein in CSF without pleocytosis). However our patient did not have the latex agglutination test. Gram stain of CSF showed large budding cells and India ink stained rounded cells with clear haloes. CSF showed cryptococci on culture. Thus normal CSF findings in HIV disease do not exclude cryptococcal meningitis if clinical suspicion is high.

An abnormal sensorium, leucocyte count in the CSF of <2.0 × 10³/l, and CSF CRAG of >1:1024 are some of the factors that place the HIV patient at higher risk of meningitis related complications and relapse. CSF antigen titres will fall with antifungal therapy, thus the latex test is useful in monitoring therapy, besides being a screening test. Occasional false positive results with the latex agglutination test could be due to rheumatoid factors and other interference factors. Rarely immune complexes with CRAG could cause artificially low titres with the use of the latex agglutination test.

Extraneural cryptococcosis commonly presents with pulmonary disease or cryptococcaemia with subacute constitutional symptoms. Though myocarditis with acute heart failure, mediastinal involvement mimicking lymphoma, cryptococcosis of the skin, eyes, and sacrum have been reported, massive and generalised cryptococcal peripheral lymphadenopathy in combination with cryptococcal meningitis, in the absence of extensive pulmonary lesions has not been reported in the medical literature. Involvement of lymph nodes is usually seen where the disease is very widely disseminated. FNAC of the cervical lymph node showed sheets of lymphocytes, histiocytes, occasional plasma cells, and macrophages. Encapsulated spherical/ovoid organisms ranging from 4–8 microns with narrow based budding were identified both intracellularly and extracellularly within the histiocytes. The yeast forms had mucicarmineophilic capsules and stained with periodic acid Schiff and Gomori’s methenamine silver. Aspirate from the lymph node showed cryptococci on culture. Thus FNAC of the lymph node is a very simple and a rapidly useful diagnostic test.
screening test in the evaluation of cryptococcal lymphadenopathy.

The figure (p 474) shows (A) soap bubble appearance of cryptococci in FNAC of lymph node, (B) polysaccharide capsule showing as clear halo around the rounded budding cryptococci in the CSF sample, (C) intracellular cryptococci budding in FNAC of lymph node, and (D) cryptococci budding (arrows) in FNAC of lymph node.

**Final diagnosis**

Advanced HIV disease with disseminated cryptococcosis, cryptococcal meningoencephalitis, generalised peripheral lymphadenopathy and oropharyngial candidiasis, and intestinal cryptosporidiosis.