RATIONAL TESTING

Investigating hypophosphataemia

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.

This article discusses common and rare causes of hypophosphataemia, appropriate investigations, and when to refer for specialist opinion

A 55 year old man with a squamous cell carcinoma of the head and neck was investigated before referral for chemotherapy. He was asymptomatic and not taking any drugs. Blood test results showed phosphate 0.7 mmol/L (reference limit 0.8-1.5) and total calcium 2.34 mmol/L (2.15-2.60).

The concentration of circulating phosphate depends on intestinal absorption, renal handling, and skeletal storage, and consequently is regulated by parathyroid hormone, vitamin D, and fibroblast growth factor 23. Internal cellular redistribution of phosphate is also important and results in hypophosphataemia under specific circumstances. The box outlines the causes of hypophosphataemia, based on the physiological regulation of phosphate metabolism.

Chronic or mild hypophosphataemia (plasma phosphate 0.6-0.8 mmol/L; 1.86-2.5 mg/dL) may be asymptomatic and therefore can be easily overlooked. A history outlining recent bone pain, muscle weakness, use of prescription drugs (including aminoglycosides, cisplatin, tenofovir), or exposure to toxins, heavy metals, or antacids containing magnesium, aluminium, and zinc, should be obtained. Inquiring about a family history of skeletal disease is important.[1] Short stature skeletal deformities consistent with rickets, such as bowed extremities, widened wrists, cranial and chest deformities, or a familial history of hypophosphataemia or rickets should alert clinicians to a heritable cause. X linked hypophosphataemic rickets is, however, rare, occurring in 1 in 20 000 live births but accounting for more than 80% of familial disease.

What are the next investigations?

The next investigations are to consider preanalytical causes or analytical interference; to measure electrolytes, including potassium, bicarbonate, magnesium, and calcium; and to assess ionised calcium, parathyroid hormone, and vitamin D under certain circumstances. The figure outlines a suggested approach to the investigation of hypophosphataemia.

Hypophosphataemia is relatively uncommon but can occur in up to 5% of patients admitted to hospital.[2] In certain clinical settings such as alcoholism, sepsis, malnutrition, or intensive care, however, the incidence of acute hypophosphataemia may be as high as 30-50%, due to a combination of phosphate redistributed between extracellular and intracellular compartments, low phosphate intake, or reduced intestinal absorption of phosphate.[3] Patients with severe hypophosphataemia (plasma phosphate <0.3 mmol/L; <0.93 mg/dL) more commonly have clinical symptoms or signs, including muscle weakness or bone pain. The diagnosis should also be considered in certain clinical circumstances: respiratory or cardiac failure, haemolysis, altered mentation, and myopathy or rhabdomyolysis, which could present with muscle pain.

Consider preanalytical causes or analytical interference

Preanalytical factors that may cause spurious hypophosphataemia include those related to biology (age), physiology (acid base or fasting status), and sampling (for example, plasma versus serum sample or delayed sample testing). Hypophosphataemia in an adult is defined as a plasma phosphate concentration of less than 0.8 mmol/L. Newborn infants and young children have a higher reference limit, and therefore age specific intervals are necessary. Spurious hypophosphataemia can occasionally occur in the presence of paraproteinaemia and transiently with respiratory alkalosis or after meals. Paraproteinaemia should be considered if the serum globulin level is increased, hypophosphataemia is severe, or there are other suspicious clinical symptoms or signs such as anaemia, renal dysfunction, bone pain, or hypercalcaemia. Light chain paraproteins are directly toxic to the renal tubule and may cause true hypophosphataemia as a result of acquired Fanconi syndrome (proximal tubulopathy resulting in failure to reabsorb phosphate as well as other nutrients). Phosphate levels are marginally lower in serum than in heparinised plasma and there is some diurnal variation, but neither accounts for major changes in phosphate concentration. Even if mild, persistent hypophosphataemia should be investigated because more serious diagnoses (such as inherited or malignant causes) could be missed. Delayed sample separation or haemolysis can falsely increase phosphate levels and mask the diagnosis of hypophosphataemia.

Case review

A plasma sample was collected from the patient after an overnight fast to retest his phosphate level. The test result was within reference limits.

The patient re-presented to an emergency department seven days after the fourth dose of chemotherapy with severe muscle pain and weakness. He was only taking paracetamol (acetaminophen). Serum creatine kinase was appreciably increased, at 4600 U/L (30-170). The patient

LEARNING POINTS

- Chronic or mild hypophosphataemia is often asymptomatic or may present with non-specific symptoms; severe cases may present with myopathy, respiratory or cardiac failure, altered mentation, haemolysis, or rhabdomyolysis
- Beware of spurious preanalytical or analytical causes of hypophosphataemia such as a non-fasting sample or paraproteinaemia
- Useful initial tests include serum electrolytes (potassium, bicarbonate, magnesium, and calcium) to assess for renal tubular disease or extrarenal causes
- Check ionised calcium, parathyroid hormone, and 25 hydroxyvitamin D if the cause is unknown or if musculoskeletal symptoms, hypomagnesaemia, or hypoalbuminaemia are present
- Referral for specialist management is advised if the cause of hypophosphataemia remains uncertain, severe (<0.3 mmol/L), or symptomatic, or if there is a family history of short stature or skeletal deformities consistent with rickets

Possible causes of hypophosphataemia

Extrarenal (common)

Gastrointestinal—reduced intestinal absorption; insufficient oral, enteral, or parenteral phosphate intake

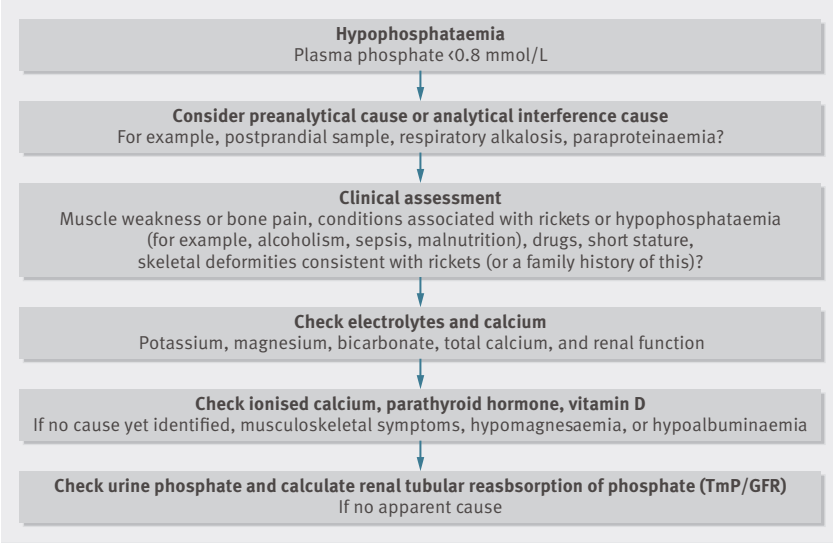
Increased intracellular sequestration (common)—refeeding syndrome; leukaemia or lymphomas; bone matrix uptake (hungry bone syndrome); diabetic ketoacidosis; respiratory alkalosis

Renal

Parathyroid hormone dependent (common)—primary, secondary, or tertiary (chronic kidney disease) hyperparathyroidism

Fibroblast growth factor 23 dependent causes (rare)—acquired (tumour induced osteomalacia) or inherited

Primary renal phosphate leak—acquired (common): drugs (for example, aminoglycosides, cisplatin, tenofovir), heavy metal poisoning or antacids containing magnesium, aluminium, or zinc), toxins, or Fanconi syndrome; inherited (rare)



Investigation algorithm for hypophosphataemia

had no history of paraesthesias or seizures and no bone tenderness or deformity on clinical examination. Other initial blood investigations included serum creatinine 89 µmol/L (60-110), estimated glomerular filtration rate 74 (90-120), phosphate 0.25 mmol/L (0.8-1.5). Severe hypophosphataemia is the most likely cause of rhabdomyolysis and this degree of hypophosphataemia makes a preanalytical cause unlikely.

Check electrolytes, including magnesium and calcium plus renal function

Serum electrolytes, magnesium, and calcium should be assessed, as renal tubular disease or extrarenal causes are common and may result in deficiencies of other electrolytes. Dietary intake of phosphate is typically more than sufficient to meet daily requirements unless severe malnutrition is present. However, chronic diarrhoea can cause hypophosphataemia by reducing intestinal absorption of phosphate, and steatorrhoea may be associated with hyperparathyroidism secondary to vitamin D deficiency resulting in parathyroid hormone induced renal phosphate wasting. Antacids that contain magnesium, zinc, or aluminium may reduce phosphate absorption by the formation of insoluble complexes.

Rapid redistribution of intracellular phosphate can cause sudden onset hypophosphataemia in certain clinical scenarios: treatment of diabetic ketoacidosis; hungry bone syndrome, which can occur after parathyroidectomy for severe hyperparathyroidism; sudden rapid cell formation, which occurs in certain haematological malignancies; and refeeding after malnutrition.[4 5] A reduced serum calcium indicates possible hungry bone syndrome.

Case review

The results of subsequent investigations were: sodium 136 mmol/L (134-146), potassium 2.6 mmol/L (3.4-5.0), bicarbonate 26 mmol/L (22-32), urea 2.8 mmol/L (3.0-8.0), creatinine 89 µmol/L (60-110), estimated glomerular filtration rate 74 (90-120), albumin 24 g/L (35-50), magnesium 0.6 mmol/L (0.7-1.1), and adjusted total calcium 2.49 mmol/L (2.15-2.60).

In this patient the degree of hypophosphataemia was severe and the coexistent less severe hypokalaemia along with hypomagnesaemia in the context of known cancer and treatment are highly suspicious of refeeding syndrome. Refeeding syndrome results in multiple changes to electrolytes that may occur when nutrition is administered after a period of low or absent oral intake. The patient's low serum urea and albumin levels reflect recent malnutrition. Electrolyte changes are more common in people with a low body mass index and prolonged malnutrition, including those with malnutrition, anorexia nervosa, HIV, chronic alcoholism, or cancer. Electrolyte changes may occur after as little as 48 hours of impaired oral intake. Enteral or parenteral carbohydrate preparations are the most common precipitants because they induce glycolysis and as a consequence there are large, sudden, and non-sustainable increased requirements for phosphate worsened by the redistribution of phosphate between extracellular and intracellular compartments. Hypophosphataemia is almost universal (>95%) in patients with refeeding syndrome; half of cases also experience hypomagnesaemia or hypokalaemia, and hypocalcaemia occurs in approximately a quarter of cases.[6] Refeeding syndrome is often clinically mild, but severe muscle weakness, paraesthesias, congestive heart failure, arrhythmias, and cardiac arrest have been described.

Check ionised calcium, parathyroid hormone, and vitamin D

When hypophosphataemia occurs in the presence of musculoskeletal symptoms, hypomagnesaemia, or hypoalbuminaemia, or the cause is still unknown, then ionised calcium, parathyroid hormone, and vitamin D should be assessed. Calcium and phosphate homeostasis are important, as both are essential for cellular function, predominantly stored in bone, and regulated by the same factors: parathyroid hormone, vitamin D, and fibroblast growth factor 23.[7]

Measurement of calcium and parathyroid hormone are important to exclude primary and secondary hyperparathyroidism, as both can present with hypophosphataemia. In case series, ionised calcium identified 25% more cases of primary hyperparathyroidism than did either total calcium or albumin adjusted total calcium, especially in the presence of major hypoalbuminaemia (as in this case), critical illness, or chronic kidney disease.[8] According to a large observational case series, approximately 10-20% of patients with primary hyperparathyroidism will have hypophosphataemia,

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Previous articles in this series

- Interpreting raised serum prolactin results (*BMJ* 2014;348:g3207)
- Using haemoglobin A1c to diagnose type 2 diabetes (*BMJ* 2014;348:g2867)
- Ordering and interpreting hepatitis B serology (*BMJ* 2014;348:g2522)
- Investigating an incidental finding of lymphopenia (*BMJ* 2014;348:g1721)
- Estimated glomerular filtration rate (*BMJ* 2014;348:g264)

although it is usually mild.[9] In a recent case series, phosphate levels were appreciably lower in patients with 25 hydroxyvitamin D (25(OH)D) <60 nmol/L and therefore concomitant vitamin D deficiency and primary hyperparathyroidism may present more commonly with hypophosphataemia.[10]

Secondary hyperparathyroidism in association with severe vitamin D deficiency leads to hypophosphataemia, hypocalcaemia, and osteomalacia, with a characteristic finding of increased alkaline phosphatase levels and muscle weakness.[11] The threshold 25(OH)D concentration that is associated with osteomalacia is debated but current consensus suggests that osteomalacia occurs with prolonged moderate or severe vitamin D deficiency (25(OH)D <30 nmol/L). Conversely, under-mineralised bone is rare when 25(OH)D concentration is >50 nmol/L.[12]

In patients with chronic kidney disease, secondary hyperparathyroidism typically occurs before appreciable changes in serum calcium or phosphate levels. In view of the respective hormonal changes and the decline in nephron mass, hypophosphataemia does not occur in early chronic kidney disease. Hypophosphataemia is, however, reported often in patients after transplantation for end stage renal disease and is attributed to autonomous parathyroid function (tertiary hyperparathyroidism).[13]

Case review

Subsequent investigations revealed: 25(OH)D 55 nmol/L (reference limit >50 nmol/L), parathyroid hormone 6.4 pmol/L (1.2-7.8), and ionised calcium 1.22 mmol/L (1.12-1.30).

An ionised calcium within reference limits helped to exclude primary parathyroid disease, especially in the presence of severe hypoalbuminaemia. Measurement of ionised calcium may not always be available in regional centres, although most tertiary hospital laboratories will offer this service. Timely analysis is required for optimal interpretation.

What subsequent specialist investigations are appropriate?

Patients need to be referred for specialist management if the cause is uncertain, hypophosphataemia is chronic, severe (phosphate <0.3 mmol/L), or symptomatic, and is accompanied by short stature or skeletal deformities consistent with rickets, or a family history of skeletal deformities or hypophosphataemia. If hypophosphataemia is mild and the diagnosis is clear, continued monitoring is appropriate in such cases. Measurement of urine phosphate with calculation of TmP/GFR (renal tubular phosphate reabsorption) is useful, and serum fibroblast growth factor 23 should be measured if TmP/GFR is reduced—that is, when renal phosphate wasting is present.

Urine phosphate and calculation of TmP/GFR

Assessment of urine phosphate excretion helps to determine if the cause is due to renal phosphate wasting. TmP/GFR requires the measurement of phosphate and creatinine in a fasting plasma sample and second voided urine sample in the morning.[14] TmP/GFR approximates the fraction of filtered phosphate that appears in the urine, is determined by nomogram or algorithm, and normative reference limits are age and sex specific, although in adults the reference limits for TmP/GFR are approximately the same as for plasma phosphate.[15] A low urine TmP/GFR indicates renal phosphate wasting, which may be due to hyperparathyroidism, increased fibroblast growth factor 23 levels, or a primary renal tubular process such as Fanconi syndrome.

Case review

This patient's result for urine TmP/GFR was >0.8 mmol/L, excluding renal phosphate wasting and supporting the diagnosis of refeeding syndrome.

Measuring fbroblast growth factor 23 if urine TmP/GFR is reduced

Fibroblast growth factor 23 is the phosphaturic substance produced by mesenchymal tumours associated with osteomalacia and the gene responsible for autosomal dominant hypophosphataemic rickets.[16] Fibroblast growth factor 23 is typically increased in tumour induced osteomalacia but low in more common causes of hypophosphataemia with renal phosphate wasting, such as drug induced tubulopathies or Fanconi syndrome (see box). The diagnosis of tumour induced osteomalacia is often delayed owing to small tumour size, scattered location, and clinical inattention to hyphophosphataemia as the cause of bone pain and muscle weakness.[15 16]

Outcome

The patient began eating a solid diet 10 days before attendance after resolution of dysphagia following chemotherapy treatment. Consequently, he represented one of the higher risk groups for refeeding syndrome. The presence of reduced albumin and urea were consistent with recent malnutrition, and the acute onset of symptomatic hypophosphataemia with rhabdomyolysis and coexistent hypokalaemia and hypomagnesaemia were consistent with refeeding syndrome. In view of the severity of hypophosphataemia and symptoms, intravenous replacement was started. Plasma phosphate and serum magnesium, potassium, and creatine kinase normalised uneventfully and muscle symptoms resolved within seven days.

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Patient consent: Patient consent not required (patient anonymised, dead, or hypothetical).

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A PATIENT'S JOURNEY

Lymphoma

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors.

Two years ago, standing in front of the bathroom mirror, I noticed that I had a right inguinal swelling. Palpation showed it to be a rubbery, mobile mass, 2.5 cm in diameter. Examining more generally, I found that I had bilateral inguinal adenopathy, the contralateral glands being only 1 cm in diameter. I was unable to palpate any cervical or axillary glands.

I was a fit 55 year old general practitioner. I was aware that the pattern was unusual, but any malignant glands that I have felt in my career have been hard and fixed. Also, like most competitive road cyclists, I shave my legs, so I hoped that the adenopathy was due to razor rash.

After a month my wife made an appointment for me to see my general practitioner, but I cancelled it as I was convinced that the swellings were getting smaller. Another month later, I realised that there had been no significant change, so I saw my general practitioner. She examined me carefully, and, even though I had felt something catch her fingers when she was palpating my left upper quadrant, it was still a surprise when she said "I think you've got a spleen." It was just palpable, halfway through deep inspiration.

Spending an hour googling "splenomegaly" and "regional adenopathy" made me realise that I had a diagnosis of lymphoma until proved otherwise. My general practitioner and consultant colleagues kindly let me organise an urgent inguinal node biopsy. Histology showed follicular lymphoma. I became anorexic and lost weight, so I assumed that I had the B type symptoms.

By the time I saw Dr Knechtli, the consultant haematologist, my appetite was returning, making me realise that my "B type" symptoms had actually been due to anxiety. However, the presence of splenomegaly on top of adenopathy in two areas suggested that I had widespread, stage IV lymphoma. The recommended management was "watchful waiting," with no advantage in beginning chemotherapy until it started to cause problems. I read that recent improvements in treatment mean that life expectancy has lengthened considerably, but, as one of the papers coyly put it, there is as yet "no levelling off of the survival curve."

My blood count was normal apart from showing lymphopenia, and the haematologist seemed pleasantly surprised that the bone marrow aspirate and trephine results showed no sign of involvement by lymphoma. However, staging computed tomography showed some mild mediastinal and abdominal lymphadenopathy. It also showed extensive nodular shadowing in my lungs, reported as being "likely to be related to lymphoma." I was inclined to accept that diagnosis and, in view of my lack of any relevant symptoms, wait until it caused problems. The haematologist, however, told me that lung infiltration was not typical of lymphoma and persuaded me to accept a respiratory referral.

The chest consultant explained that there were four possible causes of the computed tomography findings: lymphoma, infection, sarcoidosis, and "a surprise," which I took to be a euphemism for carcinoma. Bronchoscopy was normal, so I was listed for a lung biopsy. As a medical student in the late 1970s, I had spent time on a chest surgery ward and had vivid memories of patients with uncontrolled postoperative pain. To my relief, modern video-assisted thoracic surgery with excellent general and local anaesthesia, as well as nurses who ensured that I had sufficient analgesia, meant that my postoperative progress was not nearly as unpleasant as I had feared.

I was on holiday in France when the chest physician phoned with the histology: sarcoidosis. This was a huge relief. My knowledge of sarcoidosis was minimal, as I had never encountered a patient with it, so I spent a lot of time reading it up. I found that many cases, like mine, are asymptomatic, coincidental findings that may resolve spontaneously.

An interesting finding was that sarcoidosis can cause splenomegaly and inguinal adenopathy, as well as lymphopenia. I felt so well that it was difficult to believe that I had widespread lymphoma, so the overlap between the clinical findings in the two conditions made me start to question my lymphoma staging. When I saw Dr Knechtli for a follow-up appointment, I asked him whether all my clinical findings, apart from the single larger, biopsied inguinal gland, could actually be due to sarcoidosis. Unlike the haematologist, I had had two weeks to think and read up about that as a possible alternative explanation for my clinical signs. As a general practitioner, I know just how difficult it is when patients come up with a completely different way of interpreting their symptoms, and I could see in the haematologist's face his struggle to analyse the alternative diagnosis and lymphoma staging that I had sprung on him.

He agreed that my lymphoma staging was now uncertain but said that the only way to confirm it absolutely would be to have an excision biopsy of my spleen, a mediastinoscopic lymph node biopsy, and a computed tomography guided

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Previous articles in this series

- Friedreich ataxia (*BMJ* 2013;347:f7062)
- From haemochromatosis to liver transplant (*BMJ* 2013;347:f4423)
- Left atrial myxoma (*BMJ* 2013;347:f4430)
- The missing vital sign (*BMJ* 2013;347:f4163)
- Spinal injury (*BMJ* 2013;346:f3374)

biopsy of my abdominal glands. Given the risks and morbidity attached, these were not attractive options.

After discussion, I requested a biopsy of my mildly enlarged contralateral inguinal nodes. To my delight, they were reported as being reactive rather than due to lymphoma or sarcoidosis. That led me to hypothesise that all my clinical findings could be due to sarcoidosis or be reactive, apart from a single gland on the right side that had undergone lymphomatous change. If true, it would mean that I had stage I follicular lymphoma with an 80% chance of cure by radiotherapy.

Discussions with Dr Knechtli and a clinical oncologist confirmed that radiotherapy was a reasonable option. They ensured that I was aware that I may indeed have stage IV lymphoma, making a course of radiotherapy futile. However, given the "sporting chance" that I had only stage I disease, the risks and morbidity associated with the relatively low dose of treatment seemed acceptable, so I had a course of radical radiotherapy to my right hemi-pelvis.

I have been in the unusual position of having moved from an early diagnosis of stage IV (and probably incurable) follicular lymphoma to the possibility that I may have a much earlier, potentially curable stage. Because of my dual diagnoses, each of which can mimic the other, there have been 19 rate limiting steps from my initial working diagnosis to starting definitive treatment. Whereas the mean waiting time for each of them was two weeks, I needed to arrange private treatment three times to avoid considerably longer waits, and the overall nine month delay felt never ending. My observation of other European health systems suggests that the process would have been much faster in them, and I suspect that is one of the many reasons for their better cancer survival rates.

Modern evidence based treatment and superb clinical skills meant that I experienced far fewer side effects from investigations and radiotherapy than I would have experienced when I qualified in 1980. One surprise has been that, of all the clinicians who have examined me, by far the most skilled and thorough clinical examinations have been done by my general practitioner and the haematologist. That may be because they are less reliant on imaging to tell them what is going on. I would urge all my colleagues to follow their example: although in many cases clinical examination does not tell us anything unexpected, sometimes it does. My own general practitioner's knowledge that she needed to look for my spleen, and her competence in finding it, were key in accelerating my initial investigations.

A year has passed since my radiotherapy. My blood markers are back to normal; a recent scan showed a normal sized spleen and no adenopathy. Although this is encouraging, follicular lymphoma is a very slow growing malignancy. It will be some years before I know with any degree of confidence whether my "stage I" hypothesis is correct and whether the treatment was successful.

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USEFUL RESOURCES FOR PATIENTS AND CLINICIANS

Lymphoma Association (www.lymphomas.org.uk)
—A UK charity dedicated exclusively to providing specialist information and support to help lymphoma patients and their relatives, friends, and carers

British Committee for Standards in Haematology (www.bcshguidelines.com)
—Provides up to date evidence based guidelines for both clinical and laboratory haematologists on the diagnosis and treatment of haematological disease

American Society of Hematology (www.hematology.org)
—The world's largest professional society concerned with the causes and treatments of blood disorders

British Lung Foundation (www.blf.org.uk)
—Supports people affected by lung conditions including sarcoidosis, funds research, and promotes greater understanding of lung disease

Sarcoidosis Association (www.sa-uk.org)
—A British voluntary organisation dedicated to promoting and providing support to patients with sarcoidosis and their carers

Foundation for Sarcoidosis Research (www.stopsarcoidosis.org)
—A non-profit US organisation that aims to find a cure for sarcoidosis and improve the care of patients with the condition

A HAEMATOLOGIST'S PERSPECTIVE

Staging a patient's lymphoma is the most important part of the pre-treatment evaluation. In the Ann Arbor staging system, early stage lymphoma is defined by the involvement of only one group of affected lymph nodes (stage I) or of two or more affected lymph node groups on the same side of the diaphragm (stage II) in the absence of any constitutional "B" symptoms, such as unexplained weight loss, severe night sweats, or fevers. For the small minority of patients with follicular lymphoma presenting with stage I or II disease involving contiguous nodal groups and no B symptoms, the recommended management is radiotherapy to the affected areas.

However, more than 90% of patients present with more advanced stage (IIB to IVB) disease. Here, combination chemotherapy is indicated if the patient has significant symptoms, bulky disease (especially if it is compromising organ function), or impaired marrow function due to lymphomatous involvement. Such treatment is highly effective in inducing remission but is not considered to be curative.

Early chemotherapy confers no survival advantage for asymptomatic advanced stage patients, so for that group a "watch and wait" approach is usually adopted. However, evidence from a recent trial shows that such patients can benefit from the provision of weekly rituximab infusions for four weeks followed by two monthly rituximab maintenance for two years.[1]

I will confess that I initially suspected that my patient had advanced stage lymphoma with splenic involvement and lymphadenopathy on both sides of his diaphragm. However, the nodular pulmonary involvement did not fit with the usual behaviour of low grade lymphoma. I knew that establishing the cause of the pulmonary findings would require an invasive procedure. In these circumstances, it is tempting to ignore the problem, perhaps citing Occam's razor: when evaluating two hypotheses, the simpler explanation should be given preference. This can be expressed more colloquially as: "When you hear the sound of hooves, think horses not zebras." On the other hand, this runs a risk of missing dual pathology. So further investigation is merited if a feature of a patient's presentation does not fit with the working diagnosis.

Once Dr Harris's concurrent diagnosis of sarcoidosis was made, the challenge was how to establish the stage of his lymphoma. At its most thorough, and in order to avoid sampling error, this would require excision biopsies of all suspicious lymph nodes and a diagnostic splenectomy. My patient and I agreed that the potential morbidity from this approach was prohibitive. However, we agreed that if his enlarged contralateral inguinal nodes showed no involvement, this would provide some support to the hypothesis of localised lymphoma. The biopsy yielded reactive tissue, and we took a "leap of faith" with radiotherapy to his right hemi-pelvis.

We will know if we made the correct decision only after many years of follow-up. However, my confidence in Dr Harris's understanding of the complexity of the situation helped me to support the final treatment decision. Less well informed patients sometimes struggle to put all the pieces of the puzzle together without getting lost in the process.

Christopher J C Knechtli