CASE SIX

Short case number: 3_26_6
Category: Musculoskeletal System & Skin
Discipline: Medicine
Setting: General Practice
Topic: Paget's disease of bone [SDL]

Case

Vincent Bamaro, is 66 years old, he presents with a discharge letter from the local emergency department. He attended over the weekend because he had nausea and vomiting. He feels much better now, but he was asked to follow up because his one of his blood tests was abnormal. The discharge letter contains the following results.

Sodium	143	mmol/L	(135-145)
Potassium	4.2	mmol/L	(3.5-5.5)
Chloride	107	mmol/L	(95-110)
Bicarbonate	29	mmol/L	(20-32)
Urea	4.6	mmol/L	(3.0-8.0)
Creatinine	100	umol/L	(60-110)
eGFR	72		(>59)
Uric Acid	0.33	mmol/L	(0.20-0.50)
Calcium	2.27	mmol/L	(2.15-2.55)
Phosphate	0.87	mmol/L	(0.8-1.5)
Bilirubin	16	umol/L	(4-20)
ALP	*230	U/L	(35-110)
GGT	24	U/L	(5-50)
AST	21	U/L	(10-40)
ALT	20	U/L	(5-40)
Total protein	70	g/L	(68-85)
Albumin	46	g/L	(39-50)
Globulin	24	g/L	(23-39)

The request is to follow-up his abnormal serum alkaline phosphatase.

Questions

1. You consider the possible causes of the isolated abnormal ALP and think about a possible bone problem. What symptoms would you explore with Vincent? What clinical findings would support a diagnosis of Paget's disease of bone?
2. What further investigations would you undertake and why? What findings would be consistent with a diagnosis of Paget's disease?
3. Describe the radiological features of Paget's disease.
4. Vincent wants to know more about Paget's disease, because he has not had any symptoms or problems. What would you explain to Vincent about the pathophysiology of Paget's disease? What symptoms might Vincent develop if the disease progresses in his

Questions
bones? In particular what are possible consequences of Paget's disease in the skull and vertebral bodies? 5. Bisphosphonates are often used in the management of Paget's disease. Outline the mechanism of action in the treatment of this disease.

Suggested reading:

- Kumar P, Clark ML, editors. Kumar & Clark's Clinical Medicine. 9th edition. Edinburgh: Saunders Elsevier; 2016.
- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014.

ANSWERS

1. You consider the possible causes of the isolated abnormal ALP and think about a possible bone problem. What symptoms would you explore with Vincent? What clinical findings would support a diagnosis of Paget's disease of bone?

   The majority of patients are diagnosed with Paget's Disease when changes are noted incidentally on radiographs, with the most common sites of changes being pelvis, lumbar spine, femur, thoracic spine, sacrum, skull and tibia.
   Usually, the serum alkaline phosphatase is elevated.
   Symptoms when present include:
   -bone pain;
   -joint pain;
   -bone deformities in particular bowed tibia and skull changes;
   -complications of bone deformities including nerve compression, increased bone blood flow and bone fractures;

   Osteogenic sarcoma in Pagetic bone does occur but is rare. .

2. What further investigations would you undertake and why? What findings would be consistent with a diagnosis of Paget's disease?
   Investigations include:
   -Biochemisty
   Serum alkaline phosphatase is usually elevated. Bone specific alkaline phosphatase is useful if liver function tests are abnormal.
   Serum calcium, phosphorus, and parathyroid hormone levels usually remain normal.
   -Imaging studies
   Plain radiographs
   Bone scans

3. Describe the radiological features of Paget's disease.

   The radiographic appearance of Pagetic bone reflects the underlying process. Radiographs may demonstrate both osteolysis and excessive bone formation. The initial pathologic lesion, which is osteolysis, appears as radiolucency on the radiograph and is particularly evident in the skull, where it is termed osteoporosis circumscripta. Previous attempts to repair these areas are seen as areas of increased density or as coarsened trabecula. In some areas, an overt sclerotic appearance may be seen. Other relatively specific findings for Paget's disease include a classic V-shaped pattern discriminating between healthy and Pagetic bone in the long bones of the skeleton known as "the blade of grass" or "burning candle" lesion; the "brim sign," which is the thickened iliopectineal line in the pelvis. Osteoporosis circumscripta of the frontal and occipital bones of the skull and the "cotton wool" pattern in the skull are characteristic of Paget's disease reflecting the rapid bone turnover.
   Changes in the spine include enlargement of the vertebral bodies with thickened cortical shells and vertical striations produce the characteristic radiograph picture of the "framed vertebrae."

A radionuclide bone scans is the most useful way of identifying the extent of skeletal involvement. It exposes the individual to much less radiation than does a simple radiological skeletal survey. Although, radionuclide bone scans are unable to distinguish between Paget's disease and sclerotic bone metastases, they are the standard of care for identifying the extent of skeletal involvement.

4. Vincent wants to know more about Paget's disease, because he has not had any symptoms or problems. What would you explain to Vincent about the pathophysiology of Paget's disease? What symptoms might Vincent develop if the disease progresses in his bones? In particular what are possible consequences of Paget's disease in the skull and vertebral bodies?

   People without symptoms are usually diagnosed coincidentally when abnormal changes are noted on radiographs or ALP is found to be elevated. The skeletal sites most commonly involved are the pelvis, vertebral bodies, skull, femur, and tibia. Numerous active sites of skeletal involvement are more common in familial cases that tend to present early.
   The large majority of individuals diagnosed with Paget's disease of bone have NO symptoms.

   Of those with symptoms, pain is the most common presenting symptom which occurs as the result of increased bony vascularity, expanding lytic lesions, fractures, bowing, or other deformities of the extremities. Bowing of the femur or tibia will cause gait abnormalities and abnormal mechanical stresses leading to osteoarthritis of the hip or knee joints.
   Long bone bowing also causes extremity pain by stretching the muscles attached to the bone softened by the pagetic process. Back pain results from enlarged pagetic vertebrae, vertebral compression fractures, spinal stenosis, degenerative changes of the joints, and altered body mechanics with kyphosis and forward tilt of the upper back. Rarely, spinal cord compression may result from bone enlargement. Skull involvement may cause headaches, symmetric or asymmetric enlargement of the parietal or frontal bones (frontal bossing), and increased head size. Cranial expansion may narrow cranial foramina and cause neurologic complications including hearing loss from cochlear nerve damage from temporal bone involvement, cranial nerve palsies, and softening of the base of the skull (*platybasia*) allowing basilar invagination and the risk of brainstem compression. Pagetic involvement of the facial bones may cause facial deformity, loss of teeth and other dental conditions, and rarely, airway compression.
   Fractures are serious complications of Paget disease and usually occur in long bones at areas of active or advancing lytic lesions. Common fracture sites are the femoral shaft and subtrochanteric regions. Very rarely, sarcomas may complicate the changes in bone. The incidence of sarcoma appears to be decreasing, possibly because of earlier, more effective treatment with bisphosphonates.
   Cardiovascular complications may occur in patients with more than 30% of skeleton involved and very active disease as assesses by ALP levels. This may lead to arteriovenous shunting and marked increases in blood flow through the vascular pagetic bone. As a result, high-output cardiac failure may occur.

5. Bisphosphonates are often used in the management of Paget's disease. Outline the mechanism of action in the treatment of this disease.

   Bisphosphonates are the main treatment option. These agents are used because they suppress the very high rates of bone resorption and secondarily decrease the high rates of bone formation. As a result of decreasing bone turnover, pagetic structural patterns, including

areas of poorly mineralized woven bone, are replaced by more normal cancellous or lamellar bone. The improvement in skeletal structure can be demonstrated on standard radiographs and ^{99m}Tc bone scans, which show decreased isotope accumulation in pagetic sites. Reduced bone turnover can be documented by a decline in urine or serum resorption markers (pyridinoline, deoxypyridinoline, N-telopeptide, C-telopeptide) and serum markers of bone formation (ALP, serum ostase, osteocalcin).

A single intravenous dose of zoledronic acid (5 mg) can treat Paget's disease with benefit continuing for many years after a single dose. Similar efficacy had been observed after a 6-month course of alendronate 70 mg/day.