SELF ASSESSMENT ANSWERS

Calcifying cystic lesion of calcaneum

Q1: What is the differential diagnosis?

Differential diagnoses include chondromyxoid fibroma, chondroblastoma, tuberculosis, chronic sclerosing osteomyelitis, simple bone cyst, aneurysmal bone cyst, clear cell chondrosarcoma, eosinophillic granuloma, fibrous dysplasia, osteoblastoma, and giant cell tumour.

Q2: How would you proceed to confirm your diagnosis?

The first aim was to differentiate chronic infection from neoplastic bone lesions. Acid fast bacilli culture excluded a tuberculous infection. Confirmation was achieved by performing an open biopsy and histopathological examination of the specimen. The final diagnosis of chondroblastoma was confirmed in view of there being a marked cellular chondroid component rather than fibrous component in the histology slides. Thorough curettage in such cases can provide an ample diagnostic specimen as well as being a definitive treatment, and may lead to complete recovery as found in this case.

Q3: How long would you follow up this patient?

It is important to maintain regular surveillance for at least five years in such cases with a diagnosis of chondroblastoma, with a view to detect any recurrence as soon as possible. Late sarcomatous change has been reported in very rare instances.

Clinical course

Open biopsy with thorough curettage was carried out. Acid fast bacilli culture was negative. The biopsy showed a cellular infiltrate of mononuclear cells and osteoclasts with areas of formation of cartilage-like stroma. There was no finding suggestive of a malignant lesion. Histology slides were reviewed by several consultants at two specialist centre because of confusion between chondroblastoma and chondromyxoid fibroma. The final diagnosis of chondroblastoma was confirmed in view of there being a marked cellular chondroid component rather than fibrous component. Her 18 month postoperative course was uneventful.

Discussion

Chondroblastoma was described as a cartilage containing giant cell tumour by Kolodny in 1927, a calcifying giant cell tumour by Ewing in 1928, and an epiphyseal chondromatous giant cell tumour by Codman in 1931. Jaffe and Lichtenstein (1942) coined the term chondroblastoma.[1] It is a benign bone tumour composed of cells arising from chondroblasts or their precursors, which tend to differentiate into cartilage cells. It is relatively rare and represents 2% of all primary bone tumours. It occurs in the second decade of life and is primarily epiphyseal in nature. It is about twice as common in males as in females.[1] Femur, humerus, tibia, pelvis, and scapulae are the five most common bones affected by chondroblastoma. Chondroblastoma occurs in less than 1%, out of which calcaneum is affected in less than 3%. A cystic component has been found to occur in 17% and a calcifying component in 30% cases.[2 3]

Plain radiographs reveal well defined rarefaction of bone. They are usually less than 4 cm in size, eccentric, oval with smooth thin sclerotic border, with or without patchy calcification, mottling, and trabeculation.[3] In this case, we found a scalloped margin with a trabeculated appearance initially, which later on after curettage, developed a flocculent calcific cystic appearance.

MRI scans can be confusing. Heterogenous low signal intensity with lobular internal architecture and fine lobular margins with no marrow signal change and no soft tissue extension can be suggestive of chondroblastoma. It is important to look for intra-articular extension, soft tissue invasion, and malignant transformation on MRI scan. It is well known to cause a diagnostic dilemma not only at clinical and radiological levels, and even histological findings can be confusing. Normally histological examination reveals uniform densely packed round to oval cells, scanty interstitial matrix, scattered mononuclear giant cells, fibrochondroid islands, and few mitotic figures.[4 5]

Thorough curettage, with or without bone grafting, is almost always effective with an 85%–90% cure rate. Although most cases are treated successfully by conservatively performed operative procedures (such as curettage only or curettage with bone grafting), local recurrences are known to occur. These may rarely exhibit aggressive local behaviour such as extraskeletal soft tissue invasion and multifocal lesions.[5]

Final diagnosis

Calcifying cystic chondroblastoma of calcaneum.

References

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Confusion and lethargy in a 48 year old man

Q1: What does the computed tomogram show and in the light of this, what is the most appropriate investigation?

Computed tomography of the abdomen confirms hepatosplenomegaly, a small amount of ascites and small bilateral pleural effusions (fig 1; see p 242). In view of the ascites, transjugular rather than transabdominal liver biopsy should be performed. All patients should have both a coagulation screen, platelet count, and ultrasound scan of the liver performed before liver biopsy. If the prothrombin time is 4 seconds above the control value (corresponding to international normalised ratio >1.4) then the coagulopathy should be corrected before liver biopsy. Ultrasound is essential to exclude intrahepatic duct dilatation, hydatid cyst, haemangiomata, and the presence of ascites. A transjugular liver biopsy was performed without complications.

Q2: What is the histological diagnosis? List the possible causes for this

Hepatic histology demonstrates granulomatous hepatitis. There are characteristic granulomas, both intralobular and portal tract in distribution (fig 2; see p 242). One of the granulomas is large containing fibrin-like material. Ziehl-Neelsen stains for tuberculosis and periodic acid-Schiff stains for fungi were all negative. The surrounding parenchyma showed regenerative change with focal steatosis. No fibrin rings (doughnuts) or central fat vacuoles are seen. There was fibrosis around the portal tracts of a mild degree but there was no bridging fibrosis or cirrhosis. These findings are in keeping with granulomatous hepatitis.

Possible causes for granulomatous hepatitis include:

- Infections: tuberculosis, brucellosis, Q fever, syphilis, histoplasmosis, infectious mononucleosis, and AIDS.
- Drugs: sulphonamides, allopurinol, carbamezpine, quinine, and phenylbutazone.
- Others: sarcoidosis, beryllosis, primary biliary cirrhosis, and lymphoma.
- In 5%–10% no cause is found.

Q3: Can you link the histological diagnosis with the clinical history described and suggest the management of this condition?

This man presented with features of hepatic decompensation due to granulomatous hepatitis. The diagnosis was confirmed after discharge when the atypical pneumonia screen results were available. Q fever titres to the phase II antigen were greatly raised at 1280 indicating acute Q fever infection. Phase I antigen titres were less than 80. The diagnosis of Q fever is based on serology. Antibodies to the phase II antigen occur early in the course of Q fever, followed by a late rise in antibodies to the phase I antigen in the chronic state. Hepatitis is known to be associated with a high titre of antibodies to phase II antigen, as seen in this case. Q fever hepatitis usually manifests with a small increase in liver enzymes, rising to approximately twice or three times the upper limit of normal.[1] Liver involvement may occur in the absence of pulmonary involvement.[2] The association between the fibrin ring or doughnut granulomas and Q fever has been confirmed.[3] They are, however, not pathognomonic for this disease and occur in a variety of conditions including cytomegalovirus and Epstein-Barr virus infections, systemic lupus erythematosis, and allopurinol hypersensitivity. The histological response pattern to coxiella infection is often varied.

In our patient, initial testing for hepatitis C and HIV demonstrated reactive antibodies. It has been found that patients with Q fever hepatitis and endocarditis have circulating immune complexes to a component of *Coxiella burnetti*.[4] These can interfere with complement fixation antibody assays, thus producing false negative results.

Q fever is endemic in Northern Ireland, with incidence levels only second to south western England in the United Kingdom. The incidence of Q fever peaks in April to May, which can probably be in part be explained by the calving and lambing season.[2] In Northern Ireland there were six deaths between 1962 and 1989 attributable to Q fever.[5] These deaths were due to cardiac complications and one suicide. Q fever can be thought of as an occupational hazard, affecting farmers, abattoir workers, and veterinarians. However the organisms can survive for long periods in the environment, so the population as a whole is at risk. There were no occupational risk factors in this case.

Q fever is a treatable disease, with tetracyclines being the antibiotics of choice.[1] Our patient was treated initially with a two week course of oxytetracyline 500 mg four times a day, and subsequently re-treated with a further four week course in view of ongoing night sweats. He remained well at six month follow up with no significant symptoms and mildly cholestatic liver enzymes.

As our case demonstrates Q fever may cause acute hepatitis and acute liver decompensation. The diagnosis should always be considered in patients with an unexplained pyrexia and hepatitis, especially in endemic regions.

Final diagnosis

Q fever.

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A young man with weight loss and depression

Q1: What is the clinical diagnosis?

The clinical diagnosis is Cushing's syndrome. The presence of thin atrophic skin, facial plethora, hyperpigmentation over the knuckles, proximal myopathy, hypokalaemia, psychiatric symptoms, hypertension, and diabetes mellitus led to the diagnosis of Cushing's syndrome in this patient.

Q2: How should this patient be investigated?

The basal cortisol levels were raised with loss of diurnal rhythm (am: 1200 nmol/l, pm: 1200 nmol/l). The diagnosis of Cushing's syndrome was confirmed by non-suppressible serum cortisol (1200 nmol/l) with low dose dexamethasone challenge (0.5 mg every six hours for 48 hours). High evening cortisol with very inappropriately raised plasma adrenocorticotrophin (ACTH) levels (79 pmol/l) and non-suppressible serum cortisol (1200 nmol/l) with high dose dexamethasone challenge (2 mg every six hours for 48 hours) raised the possibility of an ectopic source of ACTH. Magnetic resonance imaging of the sella was done and was normal. Subsequently computed tomography of the chest and abdomen were performed. Computed tomography of the chest revealed an anterior mediastinal mass (fig 1). Computed tomography of the abdomen showed bilateral adrenal hyperplasia (fig 2). Urinary 5-hydroxyindole acetic acid was negative.

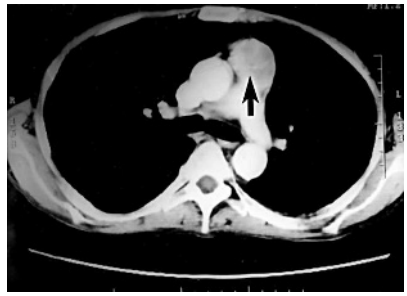

Figure 1 Contrast enhanced computed tomogram of chest showing a well circumscribed mass in the anterior mediastinum.

Q3: What are the treatment modalities available?

The treatment of choice in this patient is resection of the tumour. The tumour was found to be a thymic carcinoid on histopathological examination. Preoperatively the patient was treated with ketaconazole (1200 mg/day) and spironolactone (100 mg/day) with reduction in the dosage of antihypertensives and normalisation of serum potassium levels. After surgical resection of the tumour, the patient was able to stop taking antihypertensives and insulin and his psychiatric symptoms had abated; there was a gain in weight of 4 kg after six weeks of follow up.

Discussion

Cushing's syndrome is the result of chronic glucocorticoid excess either from endogenous hypersecretion or from exogenous therapy. The latter is the most common cause of Cushing's syndrome in clinical practice. Patients with Cushing's syndrome classically present with centripetal obesity, which is seen in 90% of the cases. Though weight gain is the rule in Cushing's syndrome, a paradoxical weight loss can be seen in a subgroup of patients, including those with a malignant tumour as the cause of Cushing's syndrome.[1] Other causes of weight loss in Cushing's syndrome are shown in box 1. Depression, uncontrolled diabetes, and the tumour itself could all have contributed to weight loss in our patient. Other manifestations of Cushing's syndrome include thin atrophic skin with easy bruisability, violaceous striae, proximal muscle weakness, hirsutism, acne, plethora, hypertension, and impaired glucose tolerance. Our patient did not have striae and easy bruisability but had severe proximal myopathy, thin atrophic skin, hypertension, and diabetes.

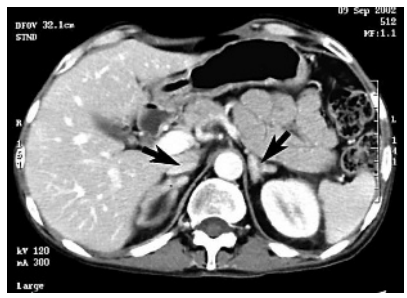

Figure 2 Contrast enhanced computed tomogram of abdomen showing bilateral adrenal hyperplasia.

Box 1: Causes of weight loss in Cushing's syndrome

- Adrenocortical carcinoma.
- Ectopic ACTH secreting tumours (small cell carcinoma of lung).
- Uncontrolled diabetes mellitus.
- Opportunistic infections (tuberculosis, systemic fungal infections).
- Severe depression.
- Associated thyrotoxicosis (McCune-Albright syndrome).

Box 2: Causes of ectopic Cushing's syndrome

- Small cell carcinoma of the lung.
- Bronchial carcinoid.
- Medullary carcinoma of the thyroid.
- Thymic carcinoid.
- Islet cell tumours.
- Pheochromocytoma.
- Ovarian tumours.

Ectopic Cushing's syndrome is seen in 15% to 20% of patients and lung tumours, including small cell carcinoma and bronchial carcinoids, account for 50% of these cases. In contrast to Cushing's disease, which has a female preponderance, ectopic Cushing's syndrome affects both sexes equally. Patients with small cell carcinoma of the lung and thymic carcinoid have a slight male preponderance.[1] Several tumours have been associated with the ectopic production of ACTH resulting in Cushing's syndrome and less commonly corticotrophin releasing hormone (box 2).

Hypokalaemic alkalosis is seen in about 15% of patients with Cushing's syndrome, particularly in those with ectopic Cushing's syndrome. Patients with ectopic Cushing's syndrome often do not have the classical clinical features of the disease. Hyperpigmentation, hypokalaemic alkalosis, and anorexia with weight loss are often seen in these patients, as in our patient.[2] This probably reflects the rapidity of the clinical course rather than atypical presentation.

Thymic carcinoid accounts for 5% to 10% of cases with ectopic Cushing's syndrome.[3] Thymic carcinoids arise from the amine precursor uptake and decarboxylation cells which can secrete a variety of peptide hormones including ACTH and corticotrophin releasing hormone. Carcinoid tumours arising from the embryonic foregut, including thymus, are deficient in the enzyme L-amino

acid decarboxylase. Therefore they have less serotonin secreting capacity and have a greater tendency for peptide hormone production. Our patient did not have the manifestation of serotonin hypersecretion and had very high ACTH levels. The clinical severity of the endocrine disease is related to the size of the tumour. The appearance of the tumour can precede, follow, or occur simultaneously with the manifestations of Cushing's syndrome.[4] As the thymic carcinoids are slow growing tumours, they may clinically and biochemically mimic pituitary Cushing's disease.[5] Up to one third of patients with thymic and bronchial carcinoids have suppressible serum cortisol with high dose dexamethasone compared with 10% of patients with other causes of Cushing's syndrome.

Surgical resection of the tumour is curative in most of the cases with thymic carcinoid. However some advocate radiotherapy postoperatively to prevent recurrence. Thymic carcinoids have varying biological behaviour with the clinical course closely related to the histological differentiation. Moran *et al* reported a five year disease-free survival of 50%, 20%, and 0% in well differentiated, moderately differentiated, and poorly differentiated tumours respectively.[6]

Final diagnosis

Ectopic Cushing's syndrome due to thymic carcinoid.

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