ORAL DISEASES

Oral Diseases (2011) 17, 238–240 doi:10.1111/j.1601-0825.2009.01548.x

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SPECIAL REVIEW

Marathon of eponyms: 16 Paget disease of bone

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The use of eponyms has long been contentious, but many remain in common use, as discussed elsewhere (Editorial: Oral Diseases. 2009: 15; 185). The use of eponyms in diseases of the head and neck is found mainly in specialties dealing with medically compromised individuals (paediatric dentistry, special care dentistry, oral and maxillofacial medicine, oral and maxillofacial pathology, oral and maxillofacial radiology and oral and maxillofacial surgery) and particularly by hospital-centred practitioners. This series has selected some of the more recognised relevant eponymous conditions and presents them alphabetically. The information is based largely on data available from MEDLINE and a number of internet websites as noted below: the authors would welcome any corrections. This document summarises data about Paget disease of bone.

Oral Diseases (2011) **17**, 238–240

Keywords: oral; eponyms; Paget disease of bone

Also known as

Paget disease
Osteitis deformans
Pozzi senile pseudorickets (misnomer)

The condition

Paget disease of bone (PDB) is a fairly common bone disorder of older males in northern Europe, but the incidence appears to be decreasing. It has been claimed that there is evidence of PDB in 4% of routine autopsies in patients over 40 years of age. The condition is almost exclusive to Anglo-Saxons.

Normal human bones continuously renew themselves, totally rebuilding approximately once every 8 years. PDB increases this turnover, with the result that the new bone is structurally disorganised, misshapen and considerably larger than normal. PDB is a focal disorder of bone re-modelling that leads to overgrowth of affected bone, with rare progression to osteosarcoma. PDB is characterised by the total disorganisation of the normally orderly remodelling of bone and an anarchic alternation of bone resorption and apposition resulting in mosaic-like 'reversal lines' often associated with severe bone pain.

Amongst the members of the tumour necrosis factor (TNF) receptor superfamily which activate nuclear factor kB (NF-kB) is RANK (receptor activator of NF-kappa B), which is involved in osteoclastogenesis. Osteoclast formation is a complex process; differentiation is dependent mainly on two cytokines – macrophage colony stimulating factor (M-CSF) and receptor activator of NF-kB ligand (RANKL) – which induce gene expression changes, presumably by inducing transcription factors.

The aetiology is unclear. Viruses, particularly paramyxoviruses such as canine distemper or measles virus, have been implicated – but with little evidence. There is a strong genetic component to PDB; 15–20% of affected people have a first-degree relative with PDB. Most patients with familial PDB have germline mutations in one of four genes involved in the RANK-NF-kB signalling pathway or its interactions with the ubiquitin-proteasome system.

Mutations in the sequestosome1 gene (SQSTM1), which encodes an important scaffold protein in RANK-NF-kB signalling pathway, have been found to be common in classical PDB and affect the ubiquitin-associated (UBA) domain of the gene product – causing loss of ubiquitin binding. SQSTM1 protein is a selective activator of the transcription factor NF-kB, which plays an important role in osteoclast differentiation and activation in response to the cytokines RANK-ligand (RANKL) and interleukin-1. TNFRSF11B gene (which encodes osteoprotegerin – a decoy receptor for RANK ligand) polymorphisms increase the risk of classical PDB, and inactivating mutations in the TNFRSF11B causes juvenile PDB.

Most kindreds with familial PDB do not carry SQSTM1 mutations. A number of rare PDB-like disorders (early-onset familial PDB, familial expansile osteolysis and expansile skeletal hyperphosphatasia) are caused by mutations in the TNFRSF11A gene, which encodes RANK.

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The rare syndrome of hereditary inclusion body myopathy, PDB and frontotemporal dementia (IBMPFD) is caused by mutations in the VCP (valosin containing protein) gene, which has a role in targeting I-kappa B (the inhibitor of NF-kB) for degradation by the proteasome.

Paget disease of bone can affect any bone, but the lumbar vertebrae and the skull are the most commonly affected. Clinical features in early lesions, where bone destruction predominates (osteolytic stage), include bowing of the long bones, especially the tibia, pathological fractures, broadening/flattening of the chest and spinal deformity. If Paget disease is widespread, the increased bone vascularity can lead to high output cardiac failure. As disease activity declines, bone apposition increases (osteosclerotic stage), bones enlarge and constriction of skull foraminae may cause cranial neuropathies. The maxilla is affected more often than the mandible.The dense bone, hypercementosis and loss of lamina dura make tooth extractions difficult, and there is a liability to haemorrhage and postoperative infection. PDB involves an increased risk of osteosarcoma. When associated with angioid streaks, the condition is known as Terry syndrome. The juvenile form of Paget disease, or familial hyperphosphatasia, is a rare recessive condition which presents with serious deformity of bones in childhood and is pathogenetically different from the adult form. IBMPFD is an autosomal dominant condition of adult onset, with degradation of the muscle system and sometimes a bone disorder and/or dementia similar to Alzheimer disease.

Paget disease of bone diagnosis is supported by imaging, biochemistry and histopathology. In early lesions, large irregular areas of relative radiolucency (osteoporosis circumscripta) are seen, but later there is increased radio-opacity, with the appearance of an irregular 'cotton wool' pattern. There is progressive thickening of the diploe and base of the skull as well as the sphenoid, orbital and frontal bones. Eventually the heavy but weak calvaria sags over the cervical spine resulting in basilar inversion and the classical 'tam-o-shanter' skull. Isotope bone scanning shows localised areas of very high uptake. Increase in plasma alkaline phosphatase and urine hydroxyproline levels, but little or no changes in serum calcium or phosphate levels, are observed. Differential diagnosis includes other fibro-osseous lesions, such as fibrous dysplasia, and conditions with a raised alkaline phosphatase, such as osteomalacia, hyperparathyroidism and osteoblastic metastatic deposits (e.g., prostate carcinoma). Bisphosphonates are the treatment of choice.

Background to eponym

The first recorded evidence of the condition was in an Egyptian skull dating to about 1000 B.C. Paget described his disease of bone osteitis deformans in 1877 in a man with progressive bone deformity, whom he had first seen in 1856. Paget described enlargement of the cranium, anterior curving of the spine, bowing of the legs, deafness and vision compromised by retinal haemorrhages. At autopsy, the bone was so soft that it could be cut by a razor, while unusual histological findings were evident.

The main person

James Paget was born on 11 January 1814, in Great Yarmouth, Norfolk, UK. He was one of 17 children born to a local brewer and shipowner. As a schoolboy, he wrote a book on the natural history of the locality. At the age of 16 years, Paget was apprenticed to Charles Costerton, a local surgeon and apothecary, and this led him to study Medicine at St. Bartholomew's Hospital, London, from 1834. During his first year as a student at St. Bartholomew's, Paget noted some white specks in the muscle of a cadaver he was dissecting and found them to be small, encapsulated worms, later named *Trichina spiralis* by Richard Owen. This was the first demonstration of human trichinosis. Paget graduated in 1836, and became a member of the Royal College of Surgeons. From 1837 to 1843, he was curator of the Royal College of Surgeons Anatomy Museum.

Paget entered private practice in 1851 and after a few years, became surgeon extraordinary to Queen Victoria and, later, surgeon ordinary to the Prince of Wales.

James Paget served as surgeon extraordinary during 1858–1877 at Bartholomew's Hospital and sergeant

Table 1 Main disorders under the name of Paget

Disorder	*Alternative name*	*Comments*
Osteitis deformans	Paget disease of bone (PDB)	See text
Inclusion Body Myopathy associated with Paget disease of bone (PDB) and Frontotemporal Dementia (FD)	IBMPFD	See text
Paget-Schrötter disease	Paget-von Schrötter disease	Deep vein thrombosis in upper limb
Extramammary Paget disease (EMPD)	Paget disease of the vulva	
Paget disease of the penis	Non-invasive adenocarcinoma	
Paget disease of the nipple	Paget disease of the breast	Rare carcinoma usually overlying an infiltrating ductal breast cancer

surgeon extraordinary during 1867–1877. He resigned from St. Bartholomew's in 1871 following an infection contracted at a postmortem. He was demonstrator of anatomy and became professor of anatomy and surgery at the Royal College of Surgeons of England (1847–1852) and was elected fellow of the Royal College of Surgeons in 1851, its vice president in 1873–1874 and president in 1875. He was honorary vice chancellor of the University of London, a member of the General Medical Council, and was doctor of honour of law at the universities of Oxford, Cambridge and Edinburgh. He was made a baronet in 1877. By 1878, he had the largest private practice in London earning £10 000 a year. He died in 1899 and his funeral was held in Westminster Abbey. Paget's fame rests on his descriptions of several diseases (Table 1).

Source internet sites (accessed 21 February 2009) and further reading

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