Paget's Disease of Bone Revisited: The Changing Indian Scenario

Classically described as a disorder in which bone remodeling has "gone awry," Paget's disease of bone (PDB) (osteitis deformans) is the paradigm of excessive osteoclastic resorption followed by secondary bone deposition by osteoblasts.[1] A focal disorder of bone metabolism, PDB, may demonstrate a monostotic or polyostotic involvement with the commonly affected bones being the skull, spine, pelvis, and long bones of the lower extremities resulting in compromised skeletal integrity. PDB may be familial or sporadic, with both genetic and environmental determinants contributing to its pathogenesis. Among the many genetic factors implicated in the causation of PDB, those directly affecting the receptor activator of nuclear factor kappa-B (RANK)-RANK ligand pathway such as mutations in the tumor necrosis factor receptor superfamily member 11A, the ubiquitin-associated locus of sequestosome 1, zinc finger protein 687, and optineurin have been associated with Paget's disease. As compared to genetic influences, there is limited information on the role of putative environmental triggers in disease causation. Few studies suggest a plausible viral etiology based on the presence of intranuclear inclusions in pagetic osteoclasts that resemble paramyxoviruses.[2]

Studies involving the incidence rates of PDB are inherently imprecise because of the paucity of symptoms in many affected individuals. Various autopsy studies and review of radiographs report the prevalence of PDB to be about 3% in countries where it is noted to be common.[3] Among the striking features concerning the epidemiology of PDB, it is worth acknowledging that its prevalence varies in different countries and even between regions within a single country.[4] Although estimates have demonstrated a declining trend of disease occurrence in the UK, the USA, and New Zealand,[5,6] it remains to be seen whether this has occurred due to an actual decrease in prevalence or as a result of an ascertainment bias due to the introduction of automated chemistry analyzers about 30 years back. The occurrence of PDB has also been reported to increase with advancing age, its prevalence reaching almost 10% by the ninth decade. Even though PDB is most often recognized after the fifth decade and more commonly in men, it may be quite presumptuous to conclude that its occurrence is rare in younger individuals, as the obvious manifestations such as skeletal deformities, bony pains, and compression syndromes tend to evolve over decades.[3]

The manifestations of this condition are seldom apparent and may not be well appreciated until secondary bone formation has become so pronounced as to cause considerable symptoms. Clinical findings range from an incidental radiological abnormality of "sclerotic-lytic" pattern of bones and an asymptomatic elevation of alkaline phosphatase to significant musculoskeletal symptoms such as bone pains, pathological fractures, macrocephaly, bony deformities, secondary osteoarthritis, compressive symptoms in the form of hearing and visual loss, vascular steal syndromes, a high-output heart failure, and osteosarcoma in <1% of affected patients.[7] A high index of suspicion is often needed to identify these clinical findings to make a diagnosis of Paget's disease. Treatment is indicated in symptomatic cases and in certain asymptomatic patients where biochemical parameters and radiological features indicate risk from untreated disease. Several agents such as bisphosphonates, calcitonin, and denosumab that inhibit osteoclastic activity are effective as therapeutic modalities in PDB. However, the Endocrine Society guidelines of 2014 and the Paget's Association guidelines of 2019 recommend the use of zoledronate as a first-choice agent in PDB.[8,9] The goals of treatment include resolution of pain and suppression of bone remodeling to allow the deposition of normal lamellar bone. Those intolerant to or unwilling for parenteral therapy may be treated with oral alendronate or risedronate for a variable duration of time. Monitoring of patients is done with serial estimation of alkaline phosphatase which gradually normalizes over 3–6 months, with normal values usually suggesting a sustained period of remission. Nonresponders may need additional doses of bisphosphonates and, occasionally, further imaging of bone lesions to rule out the concerns of a secondary neoplastic transformation.[10]

Although traditionally considered to be uncommon in Asia, PDB has been increasingly reported from the Indian subcontinent over the last two decades. In a study on 28,000 consecutive patients with diabetes, the prevalence of Paget's disease was determined to be about 0.06%.[11] In another study from southern India involving 48 patients diagnosed to have PDB, and followed up for a mean duration of 34 months, all patients treated with parenteral or oral bisphosphonates achieved clinical resolution of symptoms and biochemical remission of disease activity. Moreover, about 20% of patients were asymptomatic at presentation. This study also reported a higher proportion of women (35%) as compared to previous studies from India, probably reflecting the greater health-seeking behavior of women in our country.[12] In this issue of the journal, Asirvatham *et al*. have studied in detail the clinical profile of 66 patients from the southern state of Tamil Nadu, diagnosed with PDB and followed up for a period of 12 months.[13] Consistent with literature, the authors have reported a male preponderance of the disease, with most patients presenting in the seventh decade of life. Most had a polyostotic

disease, and all but two patients achieved remission at the end of 1 year with a single dose of zoledronate. Further, the authors highlighted the presence of familial PDB in five patients and the occurrence of malignancy in two patients. Clinical features such as the "scalp vein sign" that occurs due to the formation of arteriovenous shunts definitely warrant careful observation.

The current series describing the clinical profile of 66 patients from Tamil Nadu, as well as the previous case series reported from Vellore and the rest of the country, definitely do testify to the fact that PDB is no longer uncommon in India, as was previously thought. Many cases diagnosed with PDB are definitely from the southern part of the country. Whether this apparent "South Indian" clustering reflects a high index of suspicion maintained by the treating physician in diagnosing this condition or an inherent genetic susceptibility of individuals from this part of the country is unclear. At this juncture, it may be reasonable to conclude that the prevalence of PDB does vary between regions within the same country. Innate genetic predisposition of various ethnic groups within the same country to PDB definitely needs to be studied further. Until such studies are available, and given the frequent subtlety of manifestations, it goes without saying that the diagnosis of PDB mandates careful attention to patient symptomatology, clinical features, characteristic radiological appearance, and elevated biochemical markers of bone turnover. Disease recurrence and occasional complications may warrant long term follow-up in some patients.[14] Nevertheless, the remarkable response in most patients in terms of clinical and biochemical remission of disease following treatment with bisphosphonates is, for the treating physician, a rewarding experience indeed.

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