Case Report

Paget's Disease of Bone in Ethnic Thai Presented with Urologic Symptoms and Misleading as Metastatic Prostate Cancer: Report of a Case with a Review of the Literature

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Paget's disease of bone is common in some parts of Europe and in countries inhabited by European emigrants. In Western Countries, Paget's bone disease is one of the priorities in differential diagnosis for elderly patients who present osteoblastic lesions, so it is unlikely to be overlooked, even though patients may present symptoms unrelated to bone lesions. However, in Asian countries where Paget's disease is rare, metastatic prostate cancer appears to be the most common cause for osteoblastic lesions, thus, the Paget's disease is unlikely to be of much concern. This may lead to undue emphasis on investigations to support the diagnosis of prostate cancer. In this report, a 69 year-old man presented pain in the right leg and difficulty urinating. The plain film showed osteoblastic lesions of the right pelvic bone and lumbar spine. The pertinent routine laboratory findings revealed increased levels of serum alkaline phosphatase 125 U/L (normal 27-86). Metastatic prostate cancer was highly suspected and investigations focused upon this, including a serum prostate specific antigen assay, a transurethral cystoscopic examination, an intravenous pyelogram, and an ultrasonogram of the prostate gland. However, all of these investigations failed to support prostate cancer. Bone biopsy was performed twice, resulting in a report supporting Paget's disease of bone. The patient was treated with alendronate for three months. Radiologic findings, six months later, showed signs of improvement. He died one year later of heart failure that could plausibly had been a cardiovascular complication of Paget's disease. Better awareness of Paget's disease in Thailand and other Asian countries should reduce the incidence of unnecessary investigations and avoid a misleading diagnosis, which could lead to inappropriate treatment for metastatic prostatic cancer and undesirable psychological impact associated with being misinformed regarding malignancy.

Keywords: *Paget's disease, Asia, Prostatic cancer, Osteoblastic lesion, Cardiovascular complication*

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Patients with Paget's disease of bone may or may not present symptoms related to bone lesions. Symptomatic cases often present bone pain, fractures or nerve compression, whereas asymptomatic cases usually present elevated levels of alkaline phosphatase[1]. Our case addressed another feature of Paget's disease, i.e., presentation of urologic symptoms unrelated to radiologically-detected blastic bone lesions that led to unnecessary investigations, and might lead to a misdiagnosis of metastatic prostate cancer, especially in countries where Paget's disease is rare.

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Case Report

During admission to our hospital for cataract surgery, a 69-year-old ethnic Thai Buddhist monk also complained of difficulty in voiding urine. The digital rectal examination revealed mild enlargement of the prostate gland. A plain film of pelvis examination was simultaneously performed and revealed osteoblastic lesions at the right pelvic bone and spine (Fig. 1). Prostate cancer with bone metastasis was initially suspected and subsequent investigations were done in order to support this diagnosis. These included a serum prostate-specific antigen (PSA) assay (0.89 ng/ml compared to the normal range of 0-4 ng/ml), ultrasound examination of the prostate gland, transurethral cystoscopy, and an intravenous pyelogram examination. All of these investigations failed to support prostate cancer. Other laboratory findings revealed elevation of alkaline phosphatase (125 U/L compared to

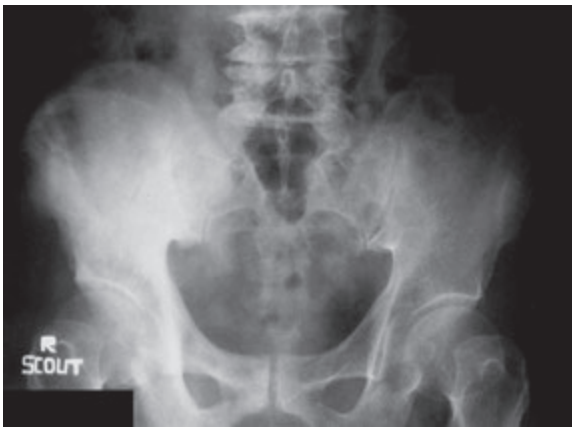

Fig. 1 Antero-posterior radiograph of the pelvis from the scout view of intravenous pyelography revealing osteosclerosis and coarse trabeculation of the right-side pelvic bones, including the ilium, ischium and pubic rami. Dense sclerosis and cortical thickening is most pronounced along the right iliopubic and ilioischial line including the subchondral region of the right sacroiliac joint. Degenerative change of the lower lumbar spine was can also be seen.

Fig. 2 Antero-posterior radiograph of the pelvis six months later revealing that the majority of the right-side pelvic bones (previously the most pronounced sclerotic area) has returned to normal density, leaving dense sclerosis only along the right iliopubic line (white arrows) and ilioischial line including the subchondral region of the right sacroiliac joint. Osteopenia can be observed at the right acetabulum and could be the effect of the bisphosphonate used for treatment.

normal 27-88 U/L), mild proteinuria + and normal routine blood electrolytes and biochemistry tests. The latter included Na 141 mM/L (normal 135-145), K 4.46 mM/L (normal 3.6-5), Cl 105 mM/L (normal 102-109), carbon dioxide 30 mM/L (normal 22.7-30.1), aspartate aminotransferase (AST) 21 U/L (normal 10-32), gamma glutamyltransferase (GGT) 42 U/L (normal 7-55), total protein 82.9 g/L (normal 70-88), albumin 52.8 g/L (normal 43-53), Ca 2.42 mM/L (normal 2.12-2.59), P 1.18 mM/L (normal 0.92-1.48), urea 6.6 mM/L (normal 2.3-7), creatinine 76 µM/L (normal 53-90), uric acid 363 µM/L (normal 200-420). Since all the investigations failed to support the diagnosis of prostate cancer, a needle core bone biopsy was performed with the expectation of metastatic prostate cancer. Instead, it resulted in a pathological diagnosis of Paget's disease of bone. Due to unfamiliarity with and rarity of this disease in our region, the clinicians doubted the diagnosis of Paget's disease and questioned whether the quantity of tissue examined was sufficient to exclude prostate cancer. As a result, an open biopsy of bone was subsequently carried out in order to obtain more tissue for the pathological examination. Again, diagnosis of Paget's disease of bone resulted with emphasis that adequate tissue had been examined to exclude a diagnosis of metastatic cancer. Thus, the patient was treated for Paget's disease with a daily oral dose of 10 mg of alendronate (fosamax) for three months. The follow-up plain film of pelvic bone six months later showed signs of normalization (Fig. 2). He was subsequently lost to follow-up, but we were informed that he died of sudden heart failure one year later. Additional information regarding his ethnicity was that he and his mother were born in Bangkok whereas his father was born in mainland China.

Discussion

Paget's disease of bone is quite common in some parts of Europe and in countries such as Australia, New Zealand, and United States, inhabited by European emigrants[2-4]. However, it is extremely rare in Southeast Asia[5]. In Thailand, there are five reported cases of ethnic Thai patients in the literature. The first case was in 1992, and the following four cases in 2011[1,5]. It is notably that all of these cases were reported by our group. Interestingly, all including the present case were of Chinese descent. Because of its rarity and unfamiliarity for clinicians in this region, the disease may be easily misdiagnosed as metastatic cancer due to close similarity in radiologic and imaging findings[1]. In adult men, prostate cancer was the most

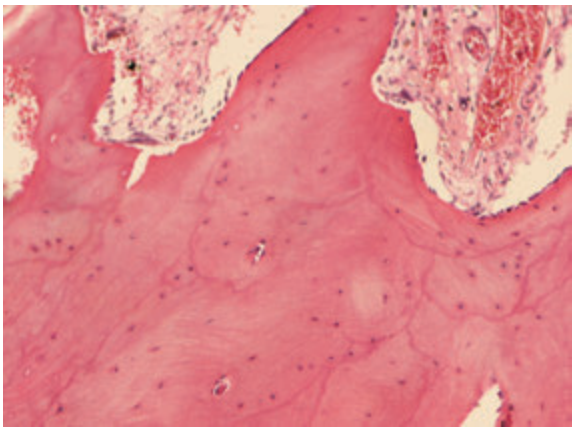

Fig. 3 Photomicrograph of biopsied bone tissue (H&E; original mag x100) showing an abnormally large number of cement-lines distributed in the bone matrix imparting a so-called "mosaic pattern". The marrow spaces contain vascularized stromata.

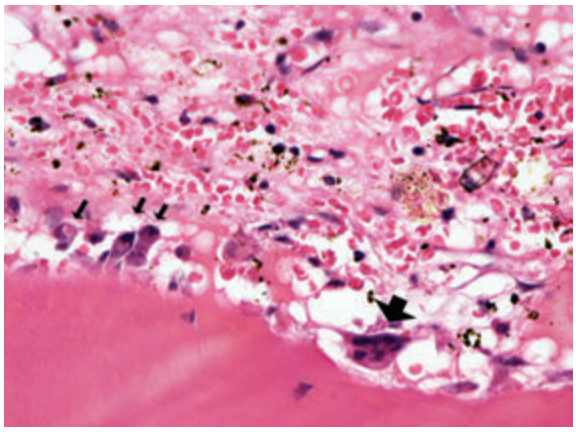

Fig. 4 Photomicrograph of biopsied bone tissue (H&E; original mag x200) showing active osteoblasts (thin arrows) and osteoclasts (thick arrow) along the interface between the bone matrix and vascularized marrow stromata.

common metastatic bone tumor and the most common metastatic tumor that produces osteoblastic lesions[6,7]. The present case was different from those previously reported that it presented confounding symptoms in contrast to symptoms related to bone lesions or no symptoms in the previous cases where investigational approaches were carried out in an appropriate direction. To our best knowledge, the presentation of blastic lesions of Paget's bone disease together with misleading symptoms resembling those of metastatic prostate cancer has not been reported from countries where Paget's bone disease is rare.

The approaches for patients that present abnormal bone lesions and urinary tract symptoms in Asian countries may be different from those in Western countries where the prevalence of Paget's disease is as high as 2% for people of 55 years or older. There, Paget's disease is likely to be suspected from the beginning when patients show radiologic indications of blastic bone lesions, regardless of other accompanying clinical symptoms. Indeed, there is a report from a western country of a case of metastatic prostate cancer being initially misdiagnosed as Paget's disease and not being properly diagnosed until after the failure of treatment for Paget's disease[8]. It is possible for the opposite to occur in Asian countries like Thailand, because of the rarity of Paget's disease and unfamiliarity with it.

In our case, many investigations were attempted to support prostate cancer, including a serum PSA assay, an ultrasound examination, transurethral cystoscopy, an intravenous pyelogram examination,

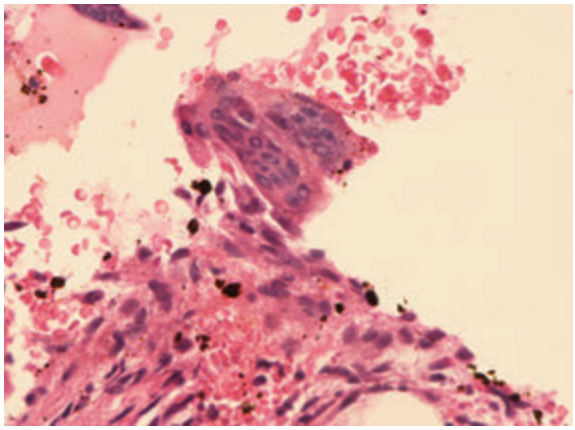

Fig. 5 Photomicrograph of biopsied bone tissue (H&E; x400) showing osteoclasts with myriad nuclei in the vascularized marrow stromata.

and repeated bone biopsy. In retrospect, we would have been able to obtain the final diagnosis of Paget's disease without performing several unnecessary investigations if we had been more aware of the possible existence of Paget's disease in our region. As a result of our experience, we recommend that Paget's disease be put in the list of differential diagnosis for elderly patients presenting osteoblastic lesions regardless of accompanying symptoms that may or may not be related to bone lesions in this geographic region. Failing to do this may result in a waste of valuable time and resources and in patients being subjected to unnecessary investigations or even subjected to improper treatment that could lead to

unexpected complications. This is to say nothing of the psychological impact for being misinformed regarding malignancy.

In Southeast Asia, there has been one report of Paget's disease of bone that was initially suspected of being metastatic prostate cancer in an 80 year old, Chinese, male patient who presented intermittent back pain. However, that case was not complicated by concomitant symptoms of urinary problems as in our presented case[9]. It is also worth mentioning that our case died of heart failure, which rarely described as a complication of Paget's disease in Asia. In the west, heart failure is one of the complications found in Paget's disease but is only encountered in about 3% of cases[10]. In the medical record, the cardiac status and underlying metabolic diseases of our patient were not addressed, so we cannot assess whether his death from cardiovascular failure could plausibly have been related to a complication of Paget's disease. In most cases of Paget's disease in our region, treatments focus mainly on the bone lesions and cardiovascular issues are not generally considered. This is probably due to unfamiliarity with the disease and its complications in addition to bone lesions. Based on our experience from this case we recommend that final diagnosis of Paget's bone disease should be followed-up immediately with evaluation of functional cardiac status in order to avoid preventable cardiovascular complications.

In conclusion, there is a reasonable risk, particularly in Asia, that patients presented with Paget's disease accompanied by lower urinary tract symptoms may be initially misdirected towards metastatic prostate cancer due to the rarity of Paget's disease in the region. This may lead to undue patient stress and to a waste of valuable time and resources on unnecessary confirmatory investigations, or even to improper treatment for metastatic prostate cancer leading to unexpected complications. Raising awareness of Paget's disease in the region may avoid these problems. Thus, we recommend for Asia that Paget's disease be put in the list of differential diagnosis for elderly patients presenting osteoblastic lesions, regardless of accompanying symptoms, and that once it is diagnosed patients be evaluated for functional cardiac status in order to avoid preventable cardiovascular complications.

What is already known on this topic?

Patients with Paget's disease of bone may or may not present symptoms related to bone lesions. Symptomatic cases often present with bone pain, fractures or nerve compression, whereas asymptomatic cases usually present with elevated levels of alkaline phosphatase[1].

What this study adds?

Our case addresses another feature of Paget's disease, i.e., presentation of urologic symptoms unrelated to radiologically-detected blastic bone lesions that led to unnecessary investigations. This information surprisingly has not been addressed in English literature. The reason why it was not addressed was probably due to the matter that the approaches for patients that present abnormal bone lesions and urinary tract symptoms in Asian countries are different from those in Western countries where the prevalence of Paget's disease is as high as 2% for people of 55 years or older. There, Paget's disease is likely to be suspected from the beginning when patients show radiologic indications of blastic bone lesions, regardless of other accompanying clinical symptoms. Indeed, there is a report from a western country of a case of metastatic prostate cancer being initially misdiagnosed as Paget's disease and not being properly diagnosed until after the failure of treatment for Paget's disease[8]. In Thailand, there are five reported cases of ethnic Thai patients in the literature. The first case was in 1992 presented with bone pain and the following four cases in 2011 presented with no symptom[1,5]. However, all of them were excessively investigated for malignancy. It is noticeable that all previously reported cases in Thailand were only from our institute and thereby the undiagnosed cases in ethnic Thai should be much more than we expected[1]. The misleading symptom as our present case should be regarded as another presentation of Paget's disease that should be aware especially for the countries where Paget's disease is rare and lead to appropriate investigations and avoid the misdiagnosis as malignancy.

Potential conflicts of interest

None.

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โรค Paget's disease ของกระดูกในผู้ป่วยไทย ซึ่งมีอาการและภาพถ่ายทางรังสีคล้ายมะเร็งต่อมลูกหมาก: รายงานผู้ป่วย 1 ราย และทบทวนวรรณกรรม

ศุภณัฐ ศิริกุลชยานนท์, สุภนีวรรณ เชาว์วิศิษฐ, วิสูตร คงเจริญสมบัติ, วรชัย ศิริกุลชยานนท์

ผู้ป่วยพระภิกษุไทย เชื้อสายจีน อายุ 64 ปี มีปัญหาเรื่องปัสสาวะขัด และมีความผิดปกติของภาพถ่ายทางรังสีวิทยาของกระดูกเชิงกรานเป็นชนิดที่มีการสร้างเนื้อกระดูกร่วมด้วย (blastic lesion) จึงให้การวินิจฉัยเบื้องต้นว่าเป็นมะเร็งของต่อมลูกหมาก ได้รับการตรวจเลือดหาระดับ PSA ตรวจต่อมลูกหมากโดยการคลำด้วยนิ้วมือ ตรวจภาพถ่ายทางรังสีของไตร่วมกับการฉีดสี ตรวจต่อมลูกหมากโดยคลื่นเสียง ผลของการตรวจทดสอบทั้งหมดไม่สามารถยืนยันได้ว่าเป็นมะเร็งของต่อมลูกหมาก จึงทำการตรวจชิ้นเนื้อกระดูกทางพยาธิวิทยา 2 ครั้ง รายงานว่าเป็น โรค Paget's disease ผู้ป่วยจึงได้รับการรักษาโดยให้ยา alendronate ภาพถ่ายทางรังสีวิทยา หลังจากรักษาได้ 6 เดือน บ่งชี้ว่าพยาธิสภาพของโรคดีขึ้น ไม่สามารถติดตามผู้ป่วยระยะยาวได้เนื่องจากผู้ป่วยเสียชีวิตจากหัวใจล้มเหลวอย่างเฉียบพลันใน 1 ปีต่อมา ซึ่งยังไม่สามารถหาสาเหตุอย่างชัดเจนได้แต่ไม่อาจตัดกรณีที่เกิดจากภาวะแทรกซ้อนของโรคนี้ได้ ผู้ป่วยสูงอายุที่มีความผิดปกติของภาพถ่ายทางรังสีของกระดูกในประเทศทางซีกโลกตะวันตก มักนึกถึงโรคนี้ร่วมด้วยเสมอในการวินิจฉัยแยกโรคจากมะเร็งที่กระจายมาที่กระดูก เพราะเป็นโรคที่พบบ่อย ส่วนในประเทศไทยพบโรคนี้น้อย แพทย์มักไม่ค่อยนึกถึงโรคนี้เลย โดยเฉพาะอย่างยิ่งเมื่อมีอาการลวงทางระบบปัสสาวะร่วมด้วย ดังที่พบในผู้ป่วยรายนี้ ผู้นิพนธ์เสนอให้ผนวกโรคนี้ในการวินิจฉัยแยกโรคในผู้ป่วยที่สงสัยมะเร็งกระจายมาที่กระดูกในผู้สูงอายุ เพื่อมิให้เกิดความผิดพลาดในการวินิจฉัยและรักษา หรือ ใช้การทดสอบที่มากเกินความจำเป็น