Usual acinar adenocarcinoma and osteoblastic lesion in the distal middle third of the femur, an unusual finding: a case report

Adenocarcinoma acinar usual e lesão osteoblástica no terço médio distal do fêmur, um achado incomum: relato de caso

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ABSTRACT
A patient with prostate cancer may initially be asymptomatic, compromising early diagnosis and treatment. A 42-year-old male patient on a routine examination had a PSA of 4.18 ng / ml. Prostate biopsy revealed usual Gleason 7 stage T2a acinar adenocarcinoma. Magnetic resonance imaging revealed a nodule in the prostate. Bone scintigraphy showed osteoblastic lesion of the left femur, considered a possibility of a secondary lesion to adenocarcinoma, but his biopsy showed tissue without significant histological changes, ruling out malignancy. The patient was submitted to a radical prostatectomy and bilateral lymphadenectomy, evolving without complications. Follow-up tests showed reactive Protein C negative, alkaline phosphatase, lactate dehydrogenase and total testosterone without changes, total PSA 0.011; Free PSA less than 0.01. The total PSA 0.3 indicated a possible recurrence after 3 years. Magnetic resonance imaging
showed no suspicious lesions, PET / CT was performed, which showed molecular hyperexpression of specific membrane antigen for the prostate, confirming local recurrence. Therefore, he was submitted to 36 radiotherapy sessions in the prostate bed from July to August. In October, the total PSA was performed, which decreased sharply. The early stage of prostate cancer may show only benign prostate growth, while the advanced stage may reveal bone pain. Bone tissue often develops a metastatic lesion, resulting in a worse prognosis. In this patient, a link between prostate carcinoma and bone lesion was ruled out by biopsy, which demonstrated the absence of spread of the disease.

**Keywords:** Adenocarcinoma; Case reports; Prostate-specific antigen.

**1 INTRODUCTION**

Prostate cancer is the second most commonly diagnosed cancer in men, with an estimated 1.1 million diagnoses worldwide in 2012, accounting for 15% of all cancers diagnosed.¹ It starts in the prostate gland, at the base of the bladder in men. It surrounds the first part of the urethra, which carries urine from the bladder. Besides that, the prostate gland helps in the production of semen, which is also carried in the urethra.²
between ages 65 and 74, 19.9% between ages 75 and 84, 4.4% at ages over 85, data collected by the National Cancer Institute, USA, within the Surveillance Epidemiology and End Results (SEER), based on the diagnosed cases from 17 geographical areas in USA monitored by SEER.³

The incidence of prostate cancer increases steeply with age, with its highest interval between ages 75-79. Prevalence: estimates from post-mortem data (no matter the cause of death) showed that half of the men aged 50-59 showed a histopathological proof of prostate cancer, and the figures went to 80% in men over 80, although only 1 in 26 (3.8%) would actually die of this disease. This is especially important when considering a population screening within asymptomatic men.³

In Brazil, there are an estimated 65,840 new cases of prostate cancer for each year of the 2020-2022 triennium. This value corresponds to an estimated risk of 62.95 new cases per 100 thousand men. Without considering non-melanoma skin tumors, prostate cancer occupies the first position in the country in all Brazilian regions.⁴

Prostate cancer can progress silently. Some have no symptoms, others have dysuria, polururia or hematuria; in the advanced stage, they may develop bone pain, generalized infection or renal failure.⁵ In the absence of symptoms, it is common for men to resist looking for a doctor, making early diagnosis and treatment difficult.⁶

Global patterns of change in incidence rates over time show the impact of PSA screening on prostate cancer epidemiology. During the past 40 years, age-adjusted incidence rates have generally increased across the world. Notably, this increasing trend has paralleled the uptake of PSA screening in certain regions, such as the United States, Europe, and Australia. The emergence of PSA screening has also led to a shift in the stage at diagnosis, with a higher proportion of men diagnosed with localized disease. However, incidence rates have also increased in regions where PSA testing has not yet been widely used, such as in Japan and some other Asian and Eastern European countries. The trend in these regions suggests that environmental or lifestyle factors may also influence prostate cancer incidence.⁷

When prostate cancer is suspected, tissue biopsy remains the standard of care for diagnosis. However, the identification and characterization of the disease have become increasingly precise through improved risk stratification and advances in magnetic resonance and functional imaging, as well as from the emergence of biomarkers.⁸

Established risk factors for total prostate cancer incidence are limited to older age, African-American race, and positive family history of prostate cancer. More recently,
genome-wide association studies (GWAS) have provided additional evidence of genetic predisposition to prostate cancer. In populations with ethnically diverse ancestry, more than 180 genetic risk loci have been confirmed. Additionally, there is probable evidence that taller height increases risk of total prostate cancer. Although these factors are not modifiable, they are illustrative of the possible mechanisms involved in prostate carcinogenesis and could be used to identify individuals at increased risk of developing this disease (risk stratification). 

In the appearance of cancer, age is the main risk factor, and it stands out in the prostate since both incidence and mortality increase exponentially after 50 years of age. Another factor is the family history of first-degree relatives with prostate cancer before the age of 60.

There are three major therapy options in localized prostate cancer: radical prostatectomy, radical radiotherapy and conservative management (only monitoring and treating the symptoms). The current approach and treatment of prostate cancer is focused not only on cancer control, but also on maintaining quality of life and minimizing the morbidity associated with different forms of treatment.

In view of the high incidence of prostate cancer, asymptomatic onset, the importance of an early diagnosis with detailed evaluation and treatment, the present study aims to report the case of a patient with usual acinar adenocarcinoma and unusual osteoblastic lesion in the distal middle third of the femur.

2 CASE REPORT

A 42-year-old patient visited the PSF in the city of Jales-SP for routine exams in August 2015. Among them, the PSA (prostate specific antigen), revealed 4.18 ng / ml, showing an increased result compared with the normal limit of 2.5ng / ml. The rest of the exams without any abnormalities. He has a family history of a father with prostate cancer at the age of 68, who underwent surgical treatment. In January 2016, the change in PSA was confirmed, showing 4.89 ng / ml.

An ecodirected biopsy of the prostate was performed in March 2016, ultrasound data showed a prostate with heterogeneous echotexture and an estimated weight of 25.2 grams (normal weight around 20 grams). Biopsy showed usual Gleason 7 (4+3) stage T2a acinar adenocarcinoma.

Magnetic resonance imaging of the abdomen and pelvis in April 2016 revealed a prostate capsule, seminal vesicles, lymph nodes, bony pelvis and bladder with normal
features, as well as liver, vesicle, spleen, pancreas, adrenals and kidneys within normal limits, the only change found it was a nodule measuring 0.9 cm in the peripheral area of the prostate. On clinical examination, incipient prostatism and prostatic touch with a nodule on the right.

In May 2016, haematological evaluation, magnetic resonance imaging of the abdomen and pelvis and bone mapping were performed. Bone showed osteoblastic lesion in the distal middle third of the left femur (Figure 1). This alteration is characteristic of bone lymphoma, but without ruling out the hypothesis of secondary bone implantation of adenocarcinoma with an atypical characteristic. It was complemented by contrast-enhanced tomography that showed a heterogeneous lesion projecting into the bone marrow of the distal middle third of the left femur diaphysis, of ill-defined limits, without disruption of the bone cortex or edema in the adjacent soft tissues, of a non-specific aspect, considering the possibility of a secondary lesion to prostate adenocarcinoma. In June 2016, the biopsy of the left femur revealed bone and cartilage tissue without significant histological changes, ruling out malignancy in the material examined. This regional and systemic study showed no spread of the disease.

Figure 1 – Bone scintigraphy showed osteoblastic lesion in the distal middle third of the left femur.
The patient was submitted to a radical prostatectomy and bilateral lymphadenectomy in July 2016 at the Sírio Libanês hospital, São Paulo. The surgical intervention performed through median laparotomy using the Walsh technique consisted of a bloc removal of the prostate, periprostatic fat, seminal vesicles and iliac lymph nodes, with satisfactory urethral vesicle reconstruction and without the need for blood transfusions. During surgery, there was an absence of extra prostatic dissemination, allowing the preservation of both nervous vascular cavernous bundles. It evolved in the postoperative period without complications.

Anatomopathological examination of the removed anatomical specimen revealed the presence of Gleason score 3 + 4 prostate adenocarcinoma (10% grade 4-5 lesion), occupying 24% of the glandular volume (volume equal to 7.2 cc), bilateral, without infiltration of the capsule and periprostatic fat and with negative surgical margins. Iliac lymph nodes, seminal vesicles and neoplasia-free bladder neck, confirming the absence of extra prostatic spread of the disease.

The first follow-up tests carried out in September 2016, showed blood count within the normal range, negative C-reactive protein, alkaline phosphatase 110 U / L (10 - 240), lactate dehydrogenase 171 U / L (135-214), total testosterone 305.4 ng / L (241 - 827), total PSA 0.011 (0 to 2.5 ng / ml), free PSA less than 0.01 (less than 0.88 ng / ml) and free PSA / total PSA 0.00 (less than 20%).

In February and November 2017, the tests mentioned above were performed again and the results were within the reference values. In April 2018, total testosterone 380, carcinoembryonic antigen 1.2 ng / ml (up to 3), free PSA 0.01 and total PSA 0.10.

In March 2019, the total PSA 0.3 indicated a possible recurrence. Bone scintigraphy was performed to rule out the connection between prostate carcinoma and the bone lesion previously identified, and resonance of the lower abdomen that showed the state after total prostatectomy without suspicious lesions. Due to the suspicion of evidenced biochemical recurrence, a thorough study was carried out at Hospital Sírio Libanês using PET / CT (positron emission tomography associated with computed tomography) that showed molecular hyperexpression of prostate-specific membrane antigen in the vesico-urethral anastomosis, indicating local recurrence (Figures 2 - 3).
Figure 2 – PET / CT (positron emission tomography associated with computed tomography) that showed molecular hyperexpression of prostate-specific membrane antigen in the vesico-urethral anastomosis

Figure 3 – PET / CT (positron emission tomography associated with computed tomography) that showed molecular hyperexpression of prostate-specific membrane antigen in the vesico-urethral anastomosis

The patient was submitted to 36 radiotherapy sessions between 06/24/2019 and 08/14/2019 in the region of the prostate bed at a dose of 7200 cGy, fractionation 200 cGy, total dose 7200 cGy.
In October 2019, total PSA after radiotherapy decreased sharply to 0.075 ng/ml and free PSA 0.01 ng/ml. Testosterone 309.0 ng/dl, lactic dehydrogenase 174.0. In March 2021, total PSA less than 0.01 ng/ml and free PSA less than 0.01 ng/ml.

3 DISCUSSION

Prostate cancer is the second most prevalent type of cancer in the male population and is among the chronic non-communicable diseases that most affect the elderly, its prevention and diagnosis are compromised by the low demand of men for health service. Several studies established that genetic factors (as “hereditary”) are involved in the aetiology of some cases of prostate cancer. A positive family history of prostate cancer has been identified as a significant risk factor in many studies. Hereditary prostate cancer is supposed to lay its basis on an altered gene (with an autosomal dominant trait) which increases a lot the susceptibility of developing the disease (with incomplete penetrance). Familial prostate cancer is supposed to be a different form of the disease, more aggressive than in the general population (due to its tendency of an early onset), being responsible for a substantial proportion of the early onset cases. The high risk given by a positive family history has emphasised the necessity of screening and early diagnosis programmes in men with a father or brother with prostate cancer. Men at elevated risk of having PCa are those > 50 years or at age > 45 years with a family history of PCa (either paternal or maternal). The patient in question was diagnosed at 42 years old and has a family history of a father with prostate cancer, a risk factor that must be considered in screening and early diagnosis programs.

Prostate cancer can grow very slowly, and symptoms may occur over several years. Symptoms include passing urine more than usual, particularly at night; needing to rush to the toilet; difficulty passing urine, including it stopping and starting; and a sense of not being able to empty the bladder fully. More unusually, there could be pain when passing urine and blood in the urine or semen. In this case, the diagnosis was at an early stage while the patient was still asymptomatic, thanks to the early screening performed with PSA.

An individualised risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis. It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it.
Retrospective analysis was performed on all patients with PCa (14,570) from the years 1994 to 2017. A total of 432 consecutive patients aged < 50 years were identified. A total of 44%, 42% and 13% of patients harboured low-risk, intermediate-risk and high-risk PCa, respectively. Their median age was 47 years and a positive family history of PCa was reported in 39.1%. Clinical stage was T1 in 65.5% and T2 in 30.0% of patients, and 2.0% of patients had metastatic disease at presentation. Radical prostatectomy (RP) was performed in 78.4% of patients (n = 339) and the biochemical recurrence rates were 7.8% (low-risk), 15.3% (intermediate-risk) and 23.3% (high-risk) at 5 years post-surgery. These rates were lower than expected according to the D'Amico prediction model or when compared with older matched patients. PCa in patients aged <50 years in the pre-PSA era was considered a virulent subtype of cancer with aggressive clinical presentation and poor prognosis. In the present large cohort of 432 patients, we found that the clinical presentation and prognosis of young patients has changed dramatically during the PSA era. Patients nowadays present with lower-risk disease that can be treated adequately, with reassuring biochemical recurrence rates at 5 years post-surgery. AS appears to be safe in patients with low-risk PCa. This shows the importance of an initial diagnosis being established in this case before the age of 50.

The objective of a tumour classification system is to combine patients with a similar clinical outcome. This allows for the design of clinical trials on relatively homogeneous patient populations, the comparison of clinical and pathological data obtained from different hospitals across the world, and the development of recommendations for the treatment of these patient populations. Throughout these Guidelines the 2017 Tumour, Node, Metastasis (TNM) classification for staging of PC.

This case presents a patient with a tumour classified as T2, tumour that is palpable and confined within the prostate and T2a, tumour involves one half of one lobe or less. In the original Gleason grading system, 5 Gleason grades (ranging from 1–5) based on histological tumour architecture were distinguished, but in the 2005 and subsequent 2014 International Society of Urological Pathology (ISUP) Gleason score (GS) modifications Gleason grades 1 and 2 were eliminated. The 2014 ISUP endorsed grading system limits the number of PCa grades, ranging them from 1 to 5, in order to: align the PCa grading with the grading of other carcinomas; eliminate the anomaly that the most highly differentiated PCas have a GS 6; to further define the clinically highly significant distinction between GS 7(3+4) and 7(4+3) PCa. When referring to Gleason, the patient’s diagnosis is 7 (4 + 3).
Prostate cancer (PCa) when progressed often develops metastasis in bone. Bone marrow is a favourite fertile soil into which prostate tumours tend to colonize and proliferate. Colonization of prostate tumour cells in bone is frequently associated with tumour-induced bone lesions. Tumour induced bone lesions generally arise from an imbalance between bone-forming osteoblasts and bone-absorbing osteoclasts induced by PCa cells. The osteoblastic bone forming lesions of PCa bone metastasis could be detected by plain radiograph, bone scan, bone biopsy, and increased levels of serum alkaline phosphatase. Histology of bone lesions shows that tumour cells are surrounded by irregular woven bone. The woven bone found in the bone metastases is structurally weak and prone to fracture. The osteoblastic bone lesions of PCa frequently contain an increased number of activated osteoblasts in the tumour-induced bone. These observations suggest a close interaction between prostate tumour cells and osteoblasts.13

Assessment of metastases: bone scan and abdominopelvic CT Because BCR after RP or RT precedes clinical metastases by 7 to 8 years on average, the diagnostic yield of common imaging techniques (bone scan and abdominopelvic CT) is low in asymptomatic patients. In men with PSA-only relapse after RP the probability of a positive bone scan is <5%, when the PSA level is <7 ng/ml. Only 11–14% of patients with BCR after RP have a positive CT.1 Metastases can be lytic, blastic or mixed. Prostate cancer is often related to blast lesions.14 The bone lesion found in the femur of this patient needed to be investigated in detail in view of the suspicion of possible bone metastasis, since this is frequent in this type of cancer, being ruled out by the absence of malignancy in the biopsy.

In this case, the treatment was with radical prostatectomy. The goal of RP by any approach is the eradication of cancer while, whenever possible, preserving pelvic organ function. The procedure involves removing the entire prostate with its capsule intact and SVs, followed by vesical-urethral anastomosis.1

Heterogeneity increases with advancing age, so it is important to use measures other than just age or performance status (PS) when considering treatment options. Individual life expectancy, health status, frailty, and co-morbidity, not only age, should be central in clinical decisions on screening, diagnostics, and treatment for PCa. A life expectancy of 10 years is most used as a threshold for benefit of local treatment.1

Whilst a rising PSA level universally precedes metastatic progression, physicians must inform the patient that the natural history of PSA-only recurrence may be prolonged and that a measurable PSA may not necessarily lead to clinically apparent metastatic. Once a PSA relapse has been diagnosed, it is important to determine whether the
recurrence has developed at local or distant sites. It should be emphasised that the treatment recommendations for these patients should be given after discussion in a multidisciplinary team.¹

The role of imaging in PSA-only recurrence imaging is only of value if it leads to a treatment change which results in an improved outcome. In practice, however, there are very limited data available regarding the outcomes consequent on imaging at relapse.¹ In this case, after PSA-only recurrence was made a bone scan and abdominopelvic CT, then a PET/CT. Treatment of PSA-only recurrences after radical prostatectomy is salvage radiotherapy for PSA-only recurrence after radical prostatectomy.¹ Following the recommendations, radiotherapy was performed after PSA-only recurrence.

4 CONCLUSION

Prostate cancer was diagnosed in this patient at 42 years of age with a positive family history, and it is necessary to discard the connection between prostate carcinoma and the identified bone lesion. This alteration has a scintigraphy characteristic of bone lymphoma, without discarding the hypothesis of secondary bone implantation of adenocarcinoma with an atypical characteristic. A biopsy revealed bone and cartilaginous tissue with no relevant histological changes, ruling out malignancy in the material examined and absence of spread of the disease. He underwent radical prostatectomy with subsequent PSA recurrence, followed by exams and rescue radiotherapy.
REFERENCES


