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Originals – Prostate cancer

Characteristics of metastatic prostate cancer occurring in patients under 50 years of age

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ARTICLE INFORMATION

ABSTRACT

Objective: To identify the clinicopathological features of metastatic prostate cancer in patients under 50 years of age.

Material and methods: A retrospective review was made of the clinical histories of patients under 50 years of age diagnosed with prostate cancer at the urology department of the National Institute for Neoplastic Diseases from 1952 to 2005. Demographic characteristics and data on history, symptoms, diagnostic procedures, treatment, and disease course were collected. Data were statistically analyzed and compared to information obtained from a literature review.

Results: There were 69 patients aged under 50 years who had been diagnosed with prostate cancer, 41 (60%) of whom had metastatic tumors. Mean patient age was 45.5 years, with a lower range of 29. All patients reported bone pain associated with other signs and symptoms such as spinal cord compression (19.5%), lower limb edema (17%), peripheral lymphadenopathies (36.5%), and abdominal tumor (2.4%). All patients had bone metastases, 14.6% had metastases in solid organs (lung and liver), 48.7% in the retroperitoneum, and 7.3% in the mediastinum. Initially, three patients were diagnosed with lymphoproliferative syndrome, one with retroperitoneal tumor of unknown etiology, and four patients with metastasis from an unknown primary tumor. Mean prostate-specific antigen (PSA) level was 795 ng/mL (3–6500). All pathologies were reported as poorly differentiated or undifferentiated. Mean survival was 16.1 months (1–84), and all patients died of disease progression.

Conclusions: Advanced prostate cancer is an uncommon condition in young adults. Its clinical presentation is atypical, as metastases may mimic other diseases. The course of disease is slow, and prognosis is poor. In patients with risk factors, PSA testing should be started before 50 years of age.

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Patrón de presentación del cáncer de próstata avanzado en pacientes menores de cincuenta años

RESUMEN

Palabras clave:
Cáncer avanzado de próstata
Adultos jóvenes
Metástasis

Objetivo: Identificar las características clínico-patológicas de presentación del cáncer de próstata avanzado en pacientes menores de 50 años.

Material y métodos: Se revisaron retrospectivamente historias clínicas de pacientes menores de 50 años con diagnóstico de cáncer de próstata avanzado del departamento de Urología del Instituto Nacional de Enfermedades Neoplásicas de 1952–2005. Se recopiló datos de filiación, antecedentes, sintomatología, métodos diagnósticos, tratamiento y evolución de la enfermedad. Se analizó estadísticamente y evaluó comparativamente con la información obtenida en la revisión de la literatura.

Resultados: Se encontraron 69 pacientes menores de 50 años con diagnóstico de cáncer de próstata de los cuales 41 (60%) fueron metastásicos. El promedio de edad fue 45,5 años con un rango inferior de 29. Todos refirieron dolor óseo, asociado a otros signos y síntomas, como compresión medular (19,5%), edema en miembros inferiores (17%), adenopatías periféricas (36,5%) y tumor abdominal (2,4%). El 100% presentaba metástasis ósea, 14,6% en vísceras sólidas (pulmón e hígado), 48,7% en retroperitoneo y 7,3% en mediastino. Inicialmente, 3 casos fueron catalogados como síndrome linfoproliferativo, uno como tumor retroperitoneal de etiología a determinar y 4 como metástasis de primario no conocido. El promedio del antígeno prostático específico fue 795 ng/ml (3–6.500). Todas las patologías fueron informadas como pobremente diferenciadas o indiferenciadas. La sobrevida promedio fue 16,1 meses (1–84), todos fallecieron por evolución de la enfermedad.

Conclusiones: El cáncer de próstata avanzado en pacientes adultos jóvenes es una patología poco frecuente. La presentación clínica no es la típica, las metástasis pueden simular otras patologías. La evolución es tórpida, con pronóstico pobre. En pacientes con factores de riesgo, se debe iniciar el estudio del antígeno prostático específico antes de los 50 años.

Introduction

Prostate cancer is a major public health problem worldwide. In the United States, 179,300 new cases and 37,000 deaths of this disease were estimated for 1999. In the European Union, 2.6 million new cases are diagnosed each year[1,2].

This condition occurs predominantly in elderly patients: 75% of new cases are diagnosed in patients older than 65 years. However, the incidence in men 50–59 years old has increased markedly since the widespread use of prostate-specific antigen (PSA) testing[4,5]. The disease is uncommon before the age of 50; there have been sporadic reports of isolated cases which are usually aggressive and respond poorly to treatment[6-14]. The National Institute for Neoplastic Diseases is the country's largest referral center for cancer; it therefore has the most cases of urologic neoplasms, including prostate cancer[3].

The present study identifies and analyzes the main clinical and pathological characteristics of this condition in patients under 50 years of age with metastatic dissemination; these characteristics are compared to data from a literature review.

Material and methods

Sample

We conducted a retrospective review of the clinical records of patients in the Department of Urology of the National Institute of Neoplastic Diseases from June 1952 to December 2005. The data collected met the following criteria: anatomopathological report of prostate cancer and age under 50 years at the time of diagnosis.

Diagnosis

The slides were reviewed by an expert pathologist in order to confirm the histopathological diagnosis; if necessary, new samples obtained from the paraffin block were examined.

Epidemiology and clinical data

The data collected included age, race, family history, duration of the disease, signs, symptoms, and physical examination.

Imaging and laboratory tests

Information from imaging techniques was corroborated by assessing the data from the medical records (X-rays, ultrasound, tomography, scintigraphy, etc.). Tumor marker data such as PSA used for diagnosis and follow-up were obtained only for cases diagnosed in the last 15 years.

Treatment

The treatment given for the primary tumor and metastases was obtained from the clinical records, and included surgery, hormone therapy, radiotherapy, and/or chemotherapy.

Anatomopathological material

The existing material was reviewed and classified per the WHO's Tumors of the Prostate chapter[15]. The Gleason score, degree of differentiation, vascular infiltration, perineural infiltration, and extraprostatic extension were assessed.

Staging

The TNM/AJCC 2002 staging system (classification of prostate carcinoma) was used, which is based on the tumor size (T), lymph node involvement (N), presence of metastasis (M), and degree of differentiation (G)[16].

Status of the disease

The date of the final follow-up visit and the status of the disease was obtained from the clinical records.

Statistical analysis

The information was codified and processed with a personal computer using the statistical package SPSS 13.0. A descriptive analysis was made, and the results were interpreted and compared to data from the literature.

Results

Prevalence

Between June 1952 and December 2005, 69 cases of prostate cancer, 41 (60%) of which were metastatic, were diagnosed in patients under the age of 50 at the National Institute for Neoplastic Diseases.

History

Only two cases (4.8%) had a first-degree family history of prostate cancer.

Age

Advanced prostate cancer in patients under 50 years of age appeared at a mean age of 45.5, with the youngest age being 29 years (fig. 1).

Clinical picture, imaging, and laboratory tests

The mean duration of the disease was 10.6 months (range: 1–36). At the first visit, 100% of patients complained of pain in the axial skeleton and other signs and symptoms such as spinal cord compression in 8 cases (19.5%), enlargement of the lower extremities in 7 cases (17%), uni-or bilateral inguinal and left cervical lymphadenopathies in 9 cases (21.9%) and 6 cases (14.6%), respectively, giant abdominal tumor in one case, and obstructive urinary symptoms in 12 cases (21.9%).

Imaging tests revealed metastasis in the retroperitoneum in 20 cases (48.7%), mediastinum in 3 cases (7.3%), liver in 4 cases (9.75%), and lung in 2 cases (4.8%). Bone metastasis was present in 100% of cases. The pathological examination revealed testicular metastasis in one patient undergoing bilateral orchiectomy (fig. 2).

Eight cases (19.5%) were initially diagnosed as non-prostatic pathology: three as lymphoproliferative syndrome, one as retroperitoneal tumor of unknown etiology, and four (9.75%) as metastasis from an unknown primary tumor.

The mean PSA in cases in which this test was done (30 patients) was 795 ng/mL (range: 3–6,500 ng/mL).

Anatomopathological characteristics

In seven cases the initial diagnosis was made with a biopsy of peripheral lymphadenopathies which reported poorly differentiated carcinoma consistent with primary prostate carcinoma.

All prostate biopsies were reported as poorly differentiated or undifferentiated. According to the current classification, the predominant Gleason score was 9 (range: 7–10).

Treatment

After diagnosis, five patients did not return, so only 36 cases (87.8%) underwent hormone therapy, which varied
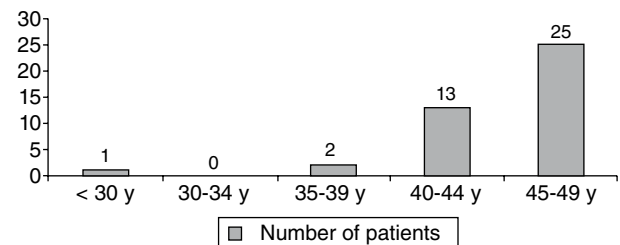

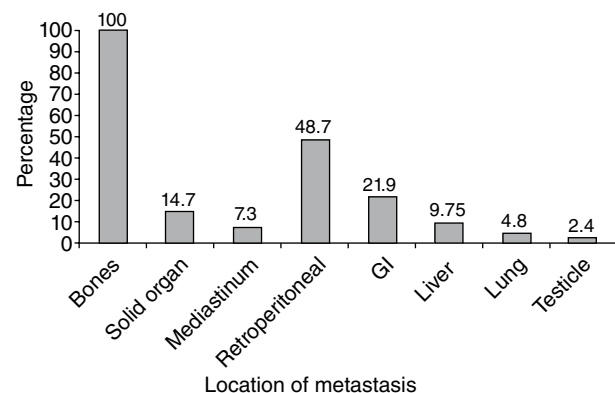Figure 1 – **Distribution of number of cases per age interval.**

Figure 2 – **Distribution of metastases.**

according to the era, and evolved from bilateral orchiectomy with adrenalectomy in the 1970s to oral and/or parenteral androgen suppression in the early years of the current decade. As the disease evolved, all patients progressively received palliative treatment of various kinds, mostly for pain, consisting of analgesic drugs, radiopharmaceuticals, and/or radiotherapy.

Status of the disease and survival

Survival from admission to the final visit or datum was on average 16.1 months, with a range of 1 to 84 months. All patients died of the disease.

Discussion

Prostate cancer is the most common malignant tumor in males; nearly one of every six men will be diagnosed with the disease at some time in their lives. It has been reported infrequently in men under the age of 50 years; a literature review shows an incidence of 0.8–1.1%[17].

Although the specific causes determining the onset and progression of prostate cancer are still unknown, there is evidence that suggests an important role of genetic and environmental factors in the course of the disease[1,2,4,5,18-20]. Approximately 8–10% of all diagnosed prostate cancers are attributable to genetic factors[1,2]. In patients with several relatives with prostate cancer and abnormalities in the HPC1 gene located in chromosome 1q24-25, Gromberg et al found the following relationship: younger age at diagnosis, higher tumor grade, and more advanced stage[18,19]. The information about the genetic component is relatively recent, for which reason probably this parameter was found in the medical records of only two cases (4.8%). Another factor is race. In epidemiological studies conducted in the United States, prostate cancer in African Americans is 1.5–2 times more frequent than in the white population[4,5].

Factors susceptible to intervention such as smoking were assessed by Roberts et al, who found that smoking in patients under 55 years of age may influence extraprostatic involvement[20]. Other relevant factors are diet and obesity. A fat-rich diet is associated with high levels of circulating androgens, which constitute a higher risk of prostate cancer. In their study on obesity, Rohrmann et al found a higher risk for high grade disease when the body mass index is elevated in patients under 50 years of age[21].

In our review we found a 29-year-old patient with consumptive syndrome, a 20×25 cm abdominopelvic mass, lumbar pain, and enlargement of his right lower extremity. The biopsy showed a poorly differentiated adenocarcinoma. The digital rectal examination revealed a stone-like prostate; PSA was 3.1 ng/mL, and other diagnostic tests showed multiple bone metastases. He received hormone therapy and palliative radiotherapy, and died 16 months after diagnosis. In our literature review we found the report of an 11-year-old boy with multiple metastases and rapid progression to death; after the autopsy, the authors considered that this tumor probably originated from immature basal cells of the prostate[8].

Advanced prostate cancer symptoms are varied and unspecific, and depend on the progression and location of the metastases. We found that at the time of diagnosis, all patients had bone pain which was associated with spinal cord compression in eight cases (19.5%), enlargement of the lower extremities in seven cases (17%), inguinal and cervical lymphadenopathies in nine (21.9%) and six (14.6%) cases respectively, giant abdominal tumor in one case, and obstructive urinary symptoms in 12 cases (21.9%). While the mechanism for metastasis is through Batson's paravertebral venous plexus with dissemination to the axial skeleton, especially the spinal column, pelvis, and ribs, there is also invasion of the appendicular skeleton (humerus and femur)[5,22].

Imaging tests revealed metastases in the retroperitoneum in 20 cases (48.7%), mediastinum in 3 cases (7.2%), liver in 4 cases (9.75%), and lung in 2 cases (4.8%). Bone metastasis was present in 100% of cases. Most cases reported in literature are advanced, with diagnosis made with the aid of imaging techniques, laboratory tests, and the anatomopathological examination of biopsies of metastases (peripheral lymphadenopathies) and/or of the prostate. For example, the cases published by Ahn et al include one 34-year-old patient with generalized lymphadenopathies that originally mimicked malignant lymphoma; Kanto et al reported the case of a 43-year-old patient with abnormal images in his chest X-rays that first looked like primary lung cancer[10,12].

The first reports on the utility of PSA appeared in the 1980s. In our study, the mean PSA in the 30 cases in which this test was done was 795 ng/mL, with a range of 3 to 6,500 ng/mL; only two patients had levels under 4 ng/mL, and the levels for the rest were over 22 ng/mL.

Tjaden and Jonson published their experiences with 56–26 patients under the age of 50 years, respectively, and report an aggressive biologic behavior and poor response to treatment[6,7]. In contrast, after the advent of the PSA era, Smith et al published studies that concluded that patients under the age of 50 have better disease-free outcomes compared to older men[23]. Some reports have shown that the rate of recurrence is not different for young and older men[24]. More recently, studies conducted at the Johns Hopkins Hospital have shown that young men in the PSA era have better post-surgical outcomes[25,26].

Until the advent of the PSA era (late 1980s and early 1990s), most prostate cancers in young men were detected due to a symptom, a clinicopathological exam, or the abnormal result of an imaging test[27]. As a result, young men often had a more advanced disease at the time of diagnosis, for which reason their response to treatment was apparently worse. The various case reports' conclusions led to the generalized belief that prostate cancer tends to be very aggressive in men under 50 years of age, who therefore are not good candidates for surgical treatment. Most of these cases were patients with locally advanced and/or metastatic disease, for which reason the outcomes were fatal for practically all[6,7].

The PSA test is radically changing the detection of prostate cancer. For example, in the United States the number of cases

diagnosed increased by more than 30% per year in 1989–92[17]. Moreover, there are reports such as Cochran et al's, that observed an increase of up to 4% of patients detected in this age group[28].

In seven cases the initial diagnosis was made with a biopsy of peripheral lymphadenopathies which reported poorly differentiated carcinoma consistent with primary prostate carcinoma. All prostate biopsies reported poorly differentiated or undifferentiated pathology; the Gleason scores were predominantly 9/10; these data are similar to those found in literature[6-15].

Patients underwent hormone therapy, which varied depending on the era, from bilateral orchiectomy with adrenalectomy in the 1970s, to oral and/or parenteral androgen suppression in the more recent cases. As the disease evolved, treatment was progressively supplemented with palliative therapies, mostly for pain control, and consisting of analgesic drugs (NSAIDs, opioids), radiopharmaceuticals, and/or radiotherapy. There are several current studies in which chemotherapy is initiated simultaneously with hormone therapy or when the condition becomes refractory[29-31].

There are still not enough data to conclude whether PSA tests and early diagnosis improve men's "luck" and prevent the development of clinical symptoms, and/or reduce prostate cancer mortality. Moreover, some research groups are concerned that the treatment may be more harmful than beneficial for men with a condition of torpid progression. More research is needed to answer these questions, but in general, studies suggest that the disease *per se* is not necessarily more aggressive in young men.

Consequently, a diagnosis based on digital rectal examination and PSA, including its variants and parameters such as PSA velocity with cutoff points as low as 0.4 ng/mL should be recommended also to patients under the age of 50 years if there is a family history or the patient belongs to a risk group[32,33].

Definitely, there is still much to be learned about the behavior and management of this disease in this population group, and much more research should be conducted for the purpose of seeking early diagnosis and better disease-free survival.

Conflict of interest

The authors state that they have no conflicts of interest.

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