Massive Pleural Effusion Due to Metastasis of Prostate Cancer

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ABSTRACT

We describe the case of a 72-year old male with pleural effusion associated with prostate cancer. There was a previous history of tobacco smoking (pack/year: 47) and of total prostatectomy followed by external beam radiation therapy seven years previously for prostate cancer. Furthermore, he was submitted to orchiectomy plus non-steroidal anti-androgen blockage, in addition to docetaxel-based chemotherapy and prednisone. After the beginning of chemotherapy, a progressive elevation in prostate specific antigen (PSA) levels was observed. On admission, he presented with fever, weight loss, and respiratory symptoms due to a massive right pleural effusion. Fluid samples obtained by needle aspiration showed haemorrhagic exudates without malignant cells. Pleural metastasis were detected by thorax imaging studies, and biopsy samples revealed prostate adenocarcinoma as the origin of his pleural effusion. Pleural fluid was drained and talc pleurodesis was performed. This report aims to describe the occurrence of massive pleural effusion due to metastasis of prostate cancer, and emphasizes the role of pleural biopsy with immunohistochemical studies to characterize this diagnosis.

Key words: Immunohistochemistry, metastasis, pleura, pleural effusion, prostate cancer

Efusión Pleural Masiva Debido a Metástasis de Cáncer de Próstata

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RESUMEN

Se describe un hombre de 72 años con efusión pleural asociada con cáncer de próstata. Había antecedentes de tabaquismo (47 paquetes por año) así como una historia de prostatectomía radical, seguida por terapia de radiación externa, siete años antes. Además, se le sometió a orquiectomía junto con bloqueo antiandrogénico no esteroideo, además de quimioterapia a base de docetaxel y prednisona. Después de iniciada la quimioterapia, se observó una elevación progresiva en los niveles de PSA. En el momento del ingreso, el paciente presentaba fiebre, pérdida de peso, y síntomas respiratorios debidos a una efusión pleural derecha voluminosa. Las muestras de fluido obtenidas mediante punción aspirativa con aguja fina, mostraron exudados hemorrágicos sin células malignas. Se detectaron implantes pleurales con los estudios imaginológicos del tórax, y las muestras de la biopsia revelaron que el origen de su efusión pleural, era un adenocarcinoma de la próstata. Se drenó el fluido pleural, y se procedió a practicar una pleurodesis con talco. Este reporte tiene por objetivo describir la ocurrencia de la efusión pleural masiva debido a la metástasis del cáncer de la próstata, y enfatiza el papel que desempeña la biopsia pleural junto a los estudios inmunohistoquímicos a la hora de caracterizar este diagnóstico.

Palabras clave: Inmuno histoquímica, metástasis, efusión pleural, cáncer de próstata

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INTRODUCTION

Prostate cancer (PCa) is the most common non-dermatologic cancer in men, and malignancies are the second cause of pleural effusion in people older than 50 years, after congestive heart failure (1). Notwithstanding, malignant pleural effusions caused by prostate carcinoma are rarely described (2). Pleural effusions in patients with malignancies can

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follow pleural direct invasion, metastasis, decreased lymphatic drainage, lung thromboembolism, atelectasis, infections, and side-effect of the treatment; or are idiopathic, developing in concomitance with previously known malignant conditions (3–4).

CASE REPORT

This 72-year old male was admitted in February 2009 with fever, productive cough and wheezing for ten days, in addition to weight loss (12 Kg in six months). He reported high blood pressure (30 years), diabetes mellitus (6 years), alcohol use (40 years) and smoking (pack/year: 47). The history of asbestos exposure was denied. There was a past surgical history of total prostatectomy (seven years ago) for prostate adenocarcinoma (Gleason 3 + 3 = 6 and PSA 80 ng/ml) followed by external beam radiation therapy. Multiple osteoblastic metastases were noted in 2008, and the treatment consisted of bilateral subcapsular orchiectomy and non-steroidal anti-androgen blockade (flutamide, 750 mg/day). In addition, he was submitted to a chemotherapeutic schedule of docetaxel (75 mg/m^2 every three weeks) associated with prednisone (5 mg orally twice daily). The patient was symptomatic, and after the docetaxel schedule, a progressive increase of prostate specific antigen (PSA) [192 and 321 ng/ml] was observed. On admission, his body mass index (BMI) was 29.77 Kg/m^2 and, except for signs of right pleural effusion, the physical examination was unre-markable. The data from laboratory tests are shown in the Table. Chest

Table: Laboratory data of a 72-year old patient with massive pleural effusion due to metatasis of prostate cancer

Tests	Admission	Day 14	Day 30*	Normal range
Red cells	3.27	4.22	3.92	4.4–6.0 x10^{12}/mm^3
Haemoglobin	8.9	11.6	10.4	11.1–16.1 g/dL
Hematocrit	27.5	36.2	32.4	39–53%
MCV	84	86	83	80–98 fl
MCHC	32	32	32	31–36%
White cells	10.2	7.3	10.3	4.0–11.0 x10^9/mm^3
Platelets	252	262	293	150–450 x10^9/mm^3
ESR	45	83	ND	≤ 15 mm/h (1st hour)
Albumin	4.4	4.0	3.4	3.5–5.0 g/dL
Globulin	1.4	1.6	1.6	< 4.0 g/dL
Urea	59.9	26.9	28.0	< 20 mg/dL
Creatinine	2.2	1.4	1.3	< 1.3 mg/dL
AST	13.5	18.7	19.9	< 39.0 U/L
ALT	6.4	11.2	7.1	< 32.0 U/L
Calcium	1.10	1.17	1.25	1.16–1.32 mmol/L
Glucose	131	88	56	70–100 mg/dL

*Date of hospital discharge. ND: not done. MCV: mean corpuscular volume; MCHC: mean corpuscular haemoglobin concentration; ESR: erythrocyte sedimentation rate; AST: aspartate aminotransferase; ALT: alanine aminotransferase;

radiographs showed massive right-sided effusion and multiple nodules suggestive of pleural metastasis (Fig. 1). Computed tomography disclosed enlarged lymph nodes near the diaphragm and cardiac areas, and in the paratracheal

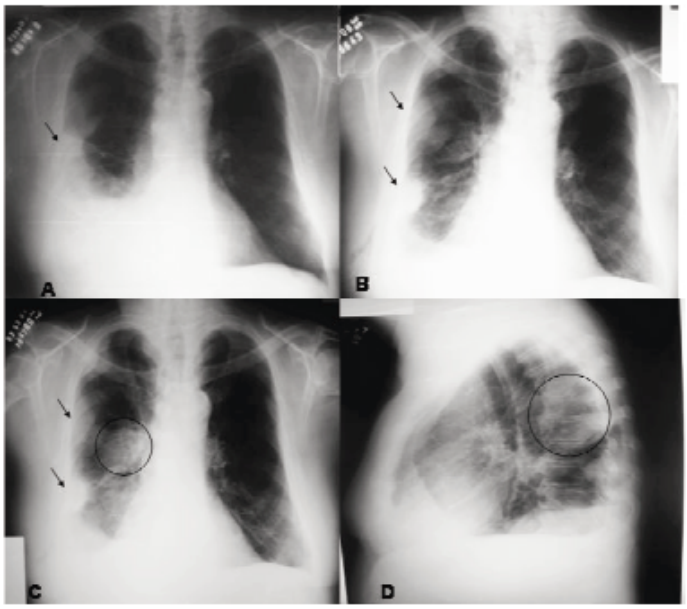

Fig. 1. A and B: Chest X-ray study showing less evident pleural metastasis (arrow) due to massive pleural effusion. The nodular metastasis appears more conspicuous after pleural drainage.
C and D: Examination of control one month later showing oval opacity (encircled) projected in the right hilar area. In the lateral view, the opacity has a posterior location.

chain; while bone metastasis were found in the ribs and vertebral bodies (Fig. 2). Pleural fluid was haemorrhagic, but

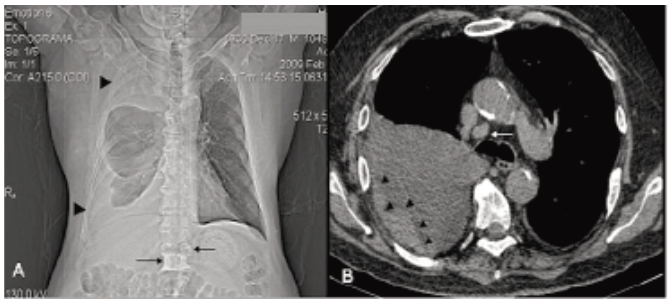

Fig. 2A: CT topogram revealing massive right pleural effusion (arrow heads), in addition to lumbar spine metastasis (arrows).
B: CT imaging of parietal pleura with irregular thickening (arrowheads) surrounded by fluid, and enlarged para tracheal lymph node measuring 12 mm in its lesser diameter (arrow).

without tumour cells. Pleural biopsy revealed an adenocarcinoma with cribriform morphology (Fig. 3A), and immunohistochemical reactions were positive for PSA and cytokeratin (CK) 7, and negative for CK20 (Figs. 3B, 3C, and 3D). Pleural metastasis of PCa was characterized, and pleural fluid drainage and talc pleurodesis were performed. Fluid sample showed: pH 7.46, white cells 55/mm^3 and red cells 11000/mm^3, total protein 3.4 g/dL, LDH 415 U/L, glucose 110 mg/dL, without either micro-organisms or malignant cells. Further evaluation for Light's criteria revealed LDH 188 U/L and total protein 5.4 mg/dL with fluid

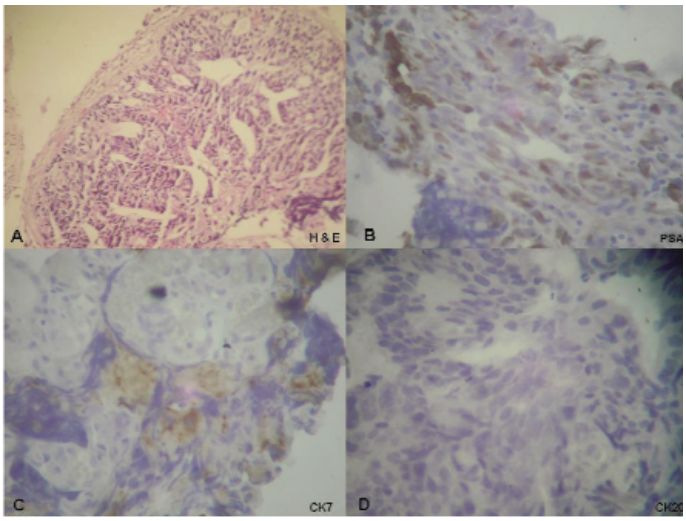

Fig. 3: A: Photomicrography of pleural sample showing nodular area with cribriform pattern indicative of prostate primary site (H and E, x 200). Immunohistochemical study:
B: Tumour cells positive for PSA (x 400).
C: Tumour cells positive for CK7 (x 400).
D: Tumour cells negative for CK20 (x400).

protein/serum protein: 0.62 and fluid LDH/serum LDH: 2.2. The PPD test was negative, and no micro-organism was grown in the urine cultures. Total and free serum PSA, and free PSA/total PSA were 485 ng/ml, 91 ng/ml, and 0.18 ng/ml, respectively. Abdominal ultrasound study showed bilateral hydronephrosis with pyelocaliceal dilation. His creatinine clearance resulted in 28 ml/min/1.73 m^2. Although indicated, the PSA could not be tested in pleural fluid samples. With clinical support, the patient improved and was discharged to home, with referrals to oncology, nephrology and pneumonology surveillance.

DISCUSSION

We describe a 72-year old male presenting with massive pleural effusion. He was a heavy smoker and alcoholic, with a previous diagnosis of PCa treated by total prostatectomy, radiation therapy, orchiectomy and non-steroidal anti-androgen use. Further progressive elevation of PSA levels occurred following docetaxel-based chemotherapy. Pleural metastases were detected by thorax imaging studies, and pleural biopsy samples with immunohistochemical studies revealed prostate adenocarcinoma as the origin of his pleural effusion. A history of neoplasm, chest X-ray and CT features, and cytologic, immunologic and microbiologic studies can raise diagnostic suspicion of malignancy in 97.7% of patients who have malignant effusions (3). Malignant effusion must be differentiated from the idiopathic cases, which have better outcomes and may appear in patients with antecedent malignancy.

Adenocarcinomas from lung, breast, ovary and stomach, in addition to lymphomas, are main causes of malignant pleural involvement (1). Primary pleural neoplasms include: diffuse or localized malignant mesothelioma, well-differentiated papillary mesothelioma, benign and malignant solitary fibrous tumour, synovial sarcoma, angiosarcoma, epithelioid hemangioendothelioma, primary effusion, lymphoma, pleuropulmonary blastoma, adenomatoid tumour, Askin tumour, histiocytoma and hemangiopericytoma, lipoma, and schwannoma. The differential diagnosis can involve pitfalls with non-neoplasm conditions, and diverse malignancies (5). Worthy of note is the co-existence of mesothelioma with other malignancies reported in 18.9% of 169 necropsies of patients with exposure to asbestos, and multiple tumours appeared synchronous in 22 of the cases. Moreover, PCa was the most frequent (7/32, 21.9%) additional malignancy found in the study (6). Despite no occupational exposure to asbestos, his pleural lesions (smaller than 4 cm in diameter) could be mistaken for class 1 mesothelioma, which was one initial hypothesis.

In this patient, pleural fluid samples revealed haemorrhagic exudates by Light's criteria, while a search for micro-organisms was negative and malignant cells were absent. A review based on fluid cytology of 103 suspected cases of malignant pleural effusions, disclosed the following origins: 1) carcinoma from lung (51.5%), breast (29.1%), liver (1.9%), stomach (1.9%), oesophagus, colon, nasopharynx, and kidney (1% each); 2) malignant mesothelioma and lymphoma (1% each); and 3) idiopathic (9.7%). Fluid cytology was positive for malignancy in 48.5% of the cases, and diagnostic yield improved with repeated sampling and pleural biopsy, while solely clinical and fluid features did not differentiate malignant from paramalignant effusions (4). Other reviews of 83 idiopathic and 263 malignant pleural effusions compared the outcomes with the biochemical fluid data. Idiopathic effusions had better outcomes (resolved in 47 and improved in 20 patients), and the authors concluded that the biochemical analysis of pleural fluid cannot predict outcomes (3). Another concern is about the aspect of malignant cells in fluid samples because in addition to typical cells of PCa, pleural fluids often contain small cells that may mimic small cell carcinoma of the lung. Moreover, PSA and prostate acid phosphatase are positive in less than 50% of the cases (2). Therefore, pleural biopsy constitutes the most useful way to clarify these diagnoses.

In the present case study, the elevation of PSA serum levels after starting docetaxel-based chemotherapy (192 to 485 ng/ml) raised the hypothesis of PSA flare (7). In fact, the patient was initially symptomatic and improved satisfactorily with the chemotherapy.

Bone and lymph nodes were also affected by PCa implants in this case. Metastases of PCa were studied in 1885 autopsies, and lung seeding occurred in 4.6% of the patients with single-organ involvement, and the frequency was 49.1% if more than two organs were involved (8). Another autopsy study of 60 patients with hormone-refractory PCa found metastases distributed in bones (95%), lymph nodes (87%) and lungs (63%), and even in widespread

cancers, the lung seeding played no role in prognosis (9). The frequency of metastasis of PCa to lumbar spine may be up to 97% (10), while pleural metastases are reported with low frequency and pleural effusions more often are associated with the high grade, high stage tumours (2). In 1589 autopsies of men older than 40 years and with PCa, bone, lung, liver, pleura and adrenal implants were found respectively in 90%, 46%, 25%, 21% and 13% of the patients (10). Metastasis of PCa can spread by vena cava or by backward pathway from prostate veins to the spine, and spine metastasis may be independent of and often precede lung metastasis (10). Massive pleural effusion occurred in the present case, and this phenomenon has been rarely described in patients without evidence of bone metastasis (11). Metastasis from other sources like lung, breast, thyroid or pancreas were differential hypotheses before the diagnosis of pleural metastasis of PCa was established.

The global increase of life expectancy can cause an increase in the incidence of PCa complications. As molecular techniques are not disposable for daily practice in developing countries, the diagnosis of metastatic PCa is according to clinical features, histological and immunohistochemical data. Worthy of note, metastatic PCa may not show reactivity for specific markers, mainly in patients with prior hormonal or radiation therapy (12–15). Novel molecular markers of PCa could not be utilized in this case study; however, in spite of prior hormonal and radiation therapy, tumour cells were positive for PSA and CK 7 markers.

The uncommon occurrence of massive pleural effusion due to local metastases of PCa is described, emphasizing the role of pleural biopsy with immunohistochemical studies to establish correct diagnoses, lessening the usual challenges in the management of these patients.

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