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Metastatic prostate cancer as an infrequent cause of fever of unknown origin, and review of the literature

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Summary. Although neoplastic fever is a rare entity, it still constitutes a clinical challenge and a troublesome symptom. Differentiating it from other cancer-related fevers, such as infection, is important for appropriate patient management. We here report on an 80 year-old patient with advanced prostate adenocarcinoma presenting with fever of unknown origin. A review of the English language literature confirms similar findings.

Key words: prostate cancer, paraneoplastic syndrome, fever of unknown origin

Introduction

Paraneoplastic syndromes often result from the release of various tumor-associated proteins rather than as a consequence of local or distant metastasis. Neoplastic fever, a paraneoplastic syndrome caused by cancer itself, represents a diagnostic challenge for the clinician and is an important issue in care of cancer patients. Although lymphoma, leukemia, and colorectal cancer are the most common malignant disorders that can cause prolonged fever, urological malignancies have also occasionally been reported.

Prostate cancer is the second most common urological malignancy to be associated with paraneoplastic syndromes after renal cell carcinoma (1), however, inflammatory paraneoplastic syndromes associated with prostatic malignancy are extremely rare entities.

Case report

An 80 year-old man was admitted with fever (up to 39°C), fatigue and asthenia of a week's duration. He had been diagnosed with prostate cancer and pelvic, liver, lung and bone metastases 1 year prior to admission. After initial remission induced by androgen blockade, the patient was being prepared for chemotherapy when he presented with an intervening fever. He was hospitalized because treatment with oral antibiotics prior to hospitalization was ineffective in controlling pyrexia.

On physical examination he had a regular peripheral pulse of 100 bpm and blood pressure of 110/70 mmHg. He was febrile with a body temperature of 39°C. There was no scleral icterus or lymphadenopathy. His systemic physical exam findings were normal apart from hepatomegaly (liver edge 7 cm below the right costal margin).

Laboratory tests revealed the following results: hemoglobin 12.9 g/dl; leukocyte count 26.000/mm^3 (predominance PMNLs); platelet count: 615.000/mm^3; CRP 265 mg/L (N: 0-5); procalcitonin (PCT) 5 ng/mL (N: 0-0.5); erythrocyte sedimentation rate (ESR) 125 mm/h; and prostate specific antigen (PSA) 438 ng/mL. Biochemical workup revealed normal liver and kidney function tests.

A diagnostic work-up consisting of blood and urine cultures, computerized tomography of the thorax, abdomen, pelvis, tuberculin skin test, and serologic assay for pathogens did not identify any infec-

tious focus or agent. Nevertheless, he was treated with broad-spectrum intravenous antibiotic combinations for up to 3 weeks during which his WBC, CRP, and PCT levels showed fluctuations. Although fever was not responsive to antibiotic treatment, it was easily controlled with nonsteroidal antiinflammatory drugs (NSAID). Therefore, advanced prostate cancer-associated systemic inflammatory syndrome was diagnosed and chemotherapy was commenced. Following chemotherapy PSA levels declined and fever subsided in two weeks. His general ambulatory performance and Eastern Cooperative Oncology Group performance status improved from 2 to 1.

Discussion

The main non-malignant causes of fever include infection, drug fever, and rheumatologic disease. Cancer is a well-recognized cause of fever, which is thought to be related to cytokines produced by the malignant cells (2). Certain tumor types including Hodgkin's disease, non-Hodgkin's lymphomas, and renal cell carcinoma are particularly associated with fever as a paraneoplastic syndrome (3).

Inflammatory cytokines have been clearly shown to have a role in progression and prognosis of prostate cancer in medical literature (4, 5). IL-6 and other chemokines play major roles in prostate carcinogenesis (5, 6). Moreover, liver metastases are a common culprit of neoplastic fever and are present in many such patients, some of whom may display significant systemic inflammation (7). Prostate cancer presenting with fever and other inflammatory markers as a paraneoplastic syndrome rarely occurs in the literature with just seven cases reported in the English language literature (PubMed/MEDLINE search; 1965-2013). Clinical characteristics of these cases are given in table 1 (8-11). The mean age of the patients was 67.8 years (range 49-81).

Fever was the initial presentation of prostate cancer in three of these, while in the others it indicated progression to castrate resistant disease. Laboratory findings showed raised inflammatory markers in all cases where data were available.

Our patient had the highest leukocyte and platelet counts, CRP, and PCT levels.

Koizumi et al. reported on a patient with prostate adenocarcinoma whose initial presentation was with fever and hemophagocytic syndrome (8).

All the patients with prostate adenocarcinoma-related systemic inflammation had stage IV disease. This finding suggests that systemic inflammation may be related to high tumor burden and a rapidly progressive course of prostate adenocarcinoma.

Fever and other related symptoms were resolved with hormonal therapy or chemotherapy in all the cases reported. However, symptoms recurred in the group receiving chemotherapy in less than a year and death eventually followed. Treatment with NSAIDs and corticosteroids might be helpful to control the inflammatory characteristics of advanced prostate cancer.

To conclude, an infectious focus should be primarily investigated in patients with systemic inflammation and prostate adenocarcinoma. An empirical regimen of broad-spectrum antibiotics for 3 days may

Table 1. Clinical characteristics of the cases.

Case No	Author [Reference]	Year published	Age	Fever onset	Stage	WBC	Platelet count (x10^3)	CRP (mg/L)	ESR (mm/h)
1	Nakamura, *et al.* (11)	1982	49	Initial	IV	9,800	217	NA	61
2	Koizumi, *et al.* (8)	2002	59	Initial	IV	7,700	54	194	NA
3	Mauri, *et al.* (10)	2005	71	Advanced	IV	7,090	228	143	126
4	Mauri, *et al.* (10)	2005	62	Advanced	IV	6,290	65	138	64
5	Mauri, *et al.* (10)	2005	75	Advanced	IV	8,090	116	130	123
6	Mauri, *et al.* (10)	2005	66	Advanced	IV	7,370	276	386	124
7	Le, *et al.* (9)	2005	81	Initial	IV	Normal	NA	NA	NA
8	Present case	2013	80	Advanced	IV	26,000	615	265	125

CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate

also be tried when the search for a focus is inconclusive. A systemic inflammation related to prostate adenocarcinoma, as a paraneoplastic syndrome, should then be considered in a patient with prolonged fever and advanced end-stage tumor when all other investigations fail and the fever responds to the NSAID test.

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