

# Rapidly Progressive Prostate Cancer in the Primary Care Setting

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Prostate cancer is the most common cause of noncutaneous cancer among men in the United States, accounting for an estimated 317,000 new cases in 1996.<sup>1</sup> Although 40,000 American men die of the disease each year, many prostatic carcinomas in the population are indolent and have limited impact on morbidity and mortality.<sup>2</sup> A small proportion of adenocarcinomas, however, are rapidly progressive, occur at younger ages, and are associated with extremely poor survival. We present the case of a relatively young and healthy patient who developed diffuse, invasive disease and the rapid onset of unusual metastatic complications within months of his diagnosis.

## Case Report

A 53-year-old white businessman came to the family practice center in December 1993 for a preventive health checkup. His only complaint was mild, intermittent lumbosacral back pain, which had been present for a number of years and was noted primarily when golfing. His medical history was otherwise unremarkable. The patient denied urinary difficulties or previous prostate disease. He stopped smoking in 1968 and drank alcohol only occasionally. There was no family history of prostate cancer. Findings on the physical examination were unremarkable with the exception of mild low-back pain with forward flexion of the spine. An area of firmness and irregularity at the left base of the prostate was found on digital examination.

Laboratory results showed multiple abnormalities (Table 1), most notably a prostate-specific antigen (PSA) value of 9340 µg/L. Needle biopsy

of the prostate revealed a diffuse, Gleason's grade 4 adenocarcinoma with a total Gleason's score of 8 in the right lobe and 9 in the left lobe. Lumbar spine radiographs disclosed diffuse sclerosis of the spine and sacroiliac region. Diffuse metastatic disease was noted on radionuclide bone imaging, with isotope uptake by the thoracic spine, ribs, pelvis, calvaria, right humerus, and femurs (Figure 1).

The patient's cancer was classified as stage D2 and treated with flutamide and monthly leuprolide acetate. At a checkup 1 month into treatment, the patient was noted to have become more severely anemic, with a hemoglobin of 6.9 g/dL (normal 14.1-18.1 g/dL). His mean corpuscular volume was 90 µm<sup>3</sup> (normal 80-97 µm<sup>3</sup>), ferritin 990 µg/L (normal 23-233 µg/L), reticulocyte count 2.2 percent (normal 0.5-1.5 percent); he had a negative Coombs test and a haptoglobin reading of 355 mg/dL (normal 19-260 mg/dL). Nucleated red blood cells as well as mild anisocytosis and poikilocytosis were found on a peripheral smear. His anemia was attributed to metastatic bone marrow infiltration and was treated with periodic red blood cell transfusions. Four months after his diagnosis, the patient's PSA value had fallen to 70 µg/L, and he continued to deny any symptoms. He was examined by an ophthalmologist for diabetic monitoring, who found no abnormalities other than an increased cup-disc ratio.

Three months later his PSA value rose to 131 µg/L, and the patient reported mild pain in the left anterior thigh. Radiographs of the left femur showed metastatic disease but no fracture. Six weeks later (about 8 months after his diagnosis), he came to the family practice center complaining of a 2-week history of blurred vision and worsening proptosis of the left eye. Magnetic resonance imaging of the head (Figure 2) showed a 2.8-cm destructive soft-tissue mass of the greater wing of the left sphenoid bone with extension into the extraconal region of the left orbit and optic canal. The mass displaced the lateral rectus

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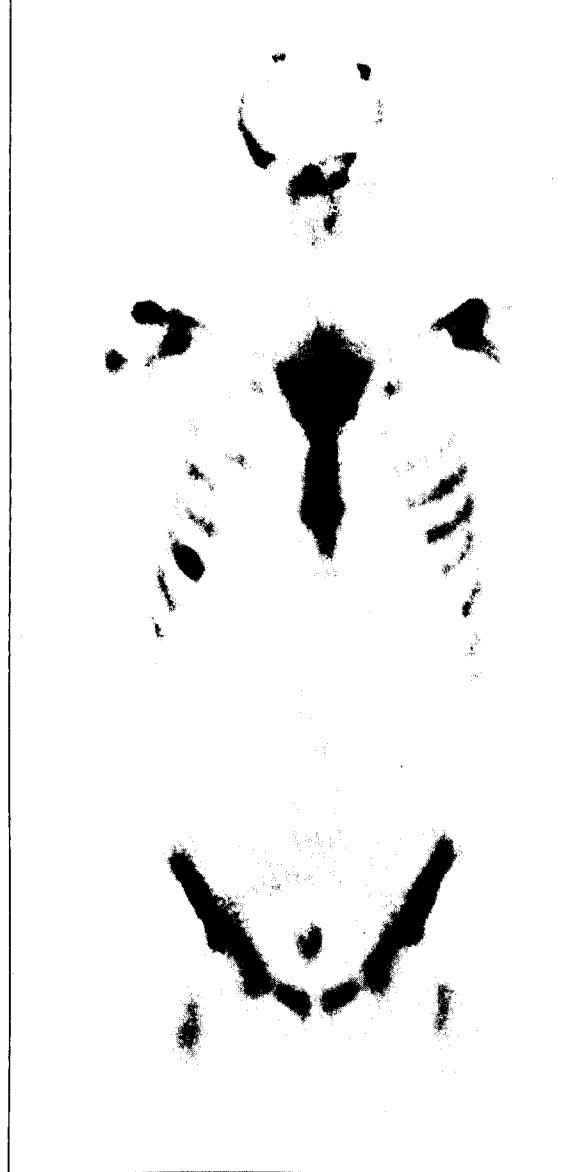
**Table 1. Relevant Abnormal Laboratory Readings From Blood Samples Taken at Initial Physician Visit.**

Laboratory Test	Patient's Test Results	Laboratory Reference Range
Prostate-specific antigen ( $\mu\text{g/L}$ )	9340	0-4.0
Platelet count ( $\times 10^3/\mu\text{L}$ )	80	140-440
Hemoglobin (g/dL)	11.8	14.1-18.1
Random plasma glucose (mg/dL)	172	70-110
Glycohemoglobin (%)	9.3	3.4-6.7
Creatinine clearance (mL/min)	61	80-120
Alkaline phosphatase (U/L)	1642	25-136
Lactic dehydrogenase (U/L)	272	89-221
Prostatic acid phosphatase (ng/mL)	5.6	0.0-2.5

muscle medially and compressed the optic nerve. The lesion was treated with radiation therapy and dexamethasone acetate. Leuprolide acetate and flutamide were discontinued, and the patient was prescribed megestrol acetate. The PSA value had risen to 434  $\mu\text{g/L}$ .

Within 2 weeks the patient reported increased lower-back, left hip, and left thigh pain; difficulty walking; and frequent falls. On physical examination he had proximal motor weakness, diminished deep tendon reflexes, and down-going toes in the left lower extremity. Radiographs and magnetic resonance imaging of the lumbar spine showed a soft-tissue mass in the L-5 vertebra, destroying the posterior vertebral cortex and compressing the left neural foramina. The patient was hospitalized for radiation therapy of the L-5 level and left orbit. High-dose intravenous diethylstilbestrol diphosphate was prescribed in combination with anticoagulants. The patient was subsequently discharged with prescriptions for oral diethylstilbestrol diphosphate and dexamethasone. He was able to walk with a cane and reported diminished musculoskeletal pain and complete resolution of his ocular symptoms. Only at this point did the patient resign from his job.

Several weeks later, about 9 months after his diagnosis, the patient was hospitalized with a left hemispheric transient ischemic attack causing dysphasia and right facial weakness. Although the acute attack resolved, the patient became paraparetic during the hospitalization. Both events

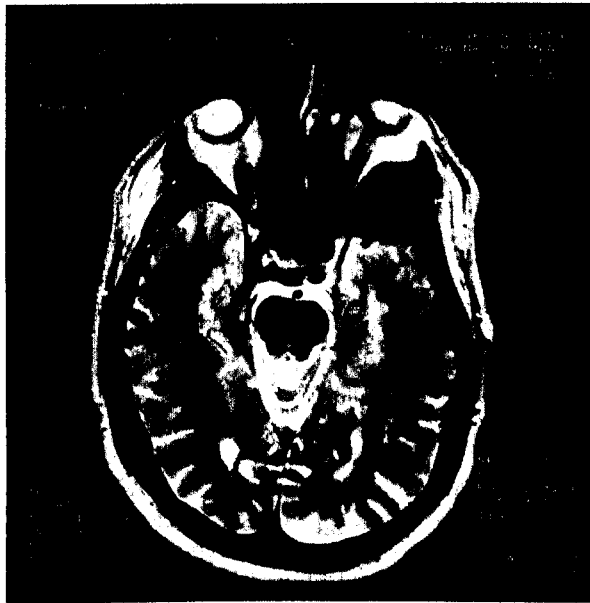


**Figure 1. Whole-body bone scan showing multifocal areas of abnormal increased uptake (ribs, skull, humerus, femurs, and pelvis) consistent with diffuse metastatic disease.**

were attributed to his hypercoagulable state. New liver metastases were diagnosed, and the patient developed pneumonia and acute nonoliguric renal failure during the hospitalization. After stabilization he was discharged to home hospice care, where he required intravenous hydration for diminished oral intake. The patient died 2 weeks later, less than 11 months after his diagnosis.

### **Discussion**

This case illustrates the insidious behavior of occult prostate cancer. With the exception of mild



**Figure 2. Magnetic resonance image of the head (T2-weighted axial sequences) showing a destructive lesion of the left lateral orbital wall.**

low-back discomfort, the patient was asymptomatic and considered himself in good health at the time of diagnosis, despite having diffuse metastatic disease. His markedly elevated PSA value (9340  $\mu\text{g/L}$ ) was unexpected in a man with minimal bone pain and no wasting. The detection of this case during a general physical examination at a family practice center emphasizes the importance of considering occult disease in apparently healthy individuals. The case also provides an important reminder of the limited predictive value of the genitourinary history in detecting cancer; the patient had no previous complaints of urinary frequency, urgency, or other voiding disorders.

Another striking feature of this case is its rapid progression in a relatively young man (aged 53 years). Although the deaths of several celebrities have publicized the lethality of prostate cancer in younger men, complications from aggressive disease are uncommon before age 65 years; only 1 percent of deaths from prostate cancer occur in men younger than 55 years.<sup>3</sup> The patient's rapid deterioration after years of symptomless disease is also noteworthy. He developed marked anemia from bone marrow infiltration 1 month after diagnosis; metastatic complications involving the femur, orbit, and lumbar spine at 7 to 8 months after diagnosis; hepatic and renal insufficiency at 9 months; and death at 11 months. Although sur-

vival from metastatic prostate cancer is poor (median survival with distant metastases is 36 to 60 months), more than 95 percent of patients in this patient's category (white, younger than 65 years, distant metastases) would have lived longer.<sup>4</sup>

References to orbital tumors and orbital metastases in the medical literature generally refer to tumors of the eye and other soft-tissue structures but also include tumors of the orbital wall. The orbital metastasis in this case is noteworthy for several reasons. First, orbital metastases are themselves uncommon, occurring in only 1 to 5 percent of patients with clinically evident metastases and 12 percent of patients who come to autopsy.<sup>5,6</sup> Fewer than 500 cases of orbital metastases have been reported in the medical literature since the first case was described in 1864. Second, prostate cancer is an infrequent source for orbital metastases, accounting for only 1 to 17 percent of such cases.<sup>6-10</sup> Prostate metastases to the skull are more likely to involve the convexity than the orbit or skull base.<sup>11</sup> Prostate cancer accounts for only about 12 percent of metastases to the skull base, and fewer than 50 cases of prostate metastases to the orbit have been reported.<sup>12-15</sup> Third, prostate metastasis to the sphenoid bone, as occurred in this case, is unusual.<sup>16</sup> Only a few cases have been reported in the literature.<sup>17-20</sup> The most common tumors to metastasize to the sphenoid bone are prostate, lung, and breast cancer.

This patient's orbital metastasis came to clinical attention because of the onset of blurred vision and proptosis. Although in this case the diagnosis of prostate cancer preceded the patient's eye complaints, about 30 to 50 percent of patients with orbital metastases have orbital symptoms before their primary tumor is diagnosed.<sup>6,10,21</sup> Orbital symptoms can precede the recognition of cancer in two thirds of patients with prostate metastases to the orbit, perhaps because of the insidious onset of prostate cancer.<sup>22</sup> The most common findings in patients with orbital metastases are diplopia, proptosis or exophthalmos, motility disturbances, and pain or headache.<sup>6,11,23</sup> Anterior lesions involving the floor, roof, and lateral walls of the orbit are more likely to cause proptosis and ophthalmoplegia. Optic nerve involvement usually occurs late in the course, probably because early tumor invasion of the orbit does not compromise the muscle cone housing the optic nerve.<sup>11</sup> Posterior orbital lesions involving the

bony walls of the orbital apex often cause simultaneous proptosis, ophthalmoplegia, and optic neuropathy.<sup>14</sup>

Although skull tumors promptly come to clinical attention when they produce orbital symptoms or cranial nerve palsies, their metastatic origin might not be apparent if an underlying malignancy is unsuspected.<sup>24</sup> Only 2 to 10 percent of orbital neoplasms are metastatic.<sup>10,21,23,25,26</sup> Clinicians should therefore consider the possibility of an underlying malignancy in patients who are at risk for such cancers and have symptoms suggestive of an orbital mass. Fine-needle aspiration or biopsy of the orbital lesion might be necessary to confirm the tissue type and can be especially important if the primary tumor has not been localized.<sup>20,27</sup> Finding tumors in the skull base can be difficult—they are usually not visible on plain radiographic films,<sup>11</sup> but the lesions can be readily recognized using computerized tomographic,<sup>28</sup> magnetic resonance,<sup>16</sup> or radionuclide imaging.

Early detection and treatment of prostate metastases to the orbit or skull base can be beneficial; they often respond to radiation or hormonal therapy, providing the patient with some relief from orbital or neuropathic symptoms.<sup>10,11,29</sup> The long-term prognosis for such patients is poor, however; reported median survival is 6 to 26 months after ophthalmic symptoms appear. Improved treatments for metastatic prostate cancer are being investigated,<sup>30</sup> but the prognosis remains poor for most patients unless the cancer is diagnosed at a less-advanced stage. The potential benefits of early detection and the ability of PSA testing to detect cancer while it is still localized have prompted some groups to recommend routine PSA screening of all men older than age 50 years.<sup>31,32</sup> Other groups<sup>31</sup> have recommended against routine screening, however, citing the lack of direct evidence that early detection and treatment reduce morbidity or mortality from the disease and uncertainty about whether the benefits of screening outweigh the potential harms associated with testing and treatment.<sup>2</sup>

In summary, the important clinical lessons from this case are that the possibility of prostate cancer should not be overlooked in younger men; that diffuse metastatic disease can be found in the primary care setting in asymptomatic patients who have no genitourinary complaints or bone pain; that prostate cancer, although often indo-

lent, can occasionally be rapidly progressive and produce acute multisystem clinical deterioration; that prostate cancer can metastasize to the orbit or skull base; and that an underlying malignancy should be considered in all patients who complain of orbital symptoms that could be due to a metastatic lesion.

## References

1. Parker SL, Tong T, Bolden S, Wingo PA. Cancer statistics, 1996. *CA: Cancer J Clin* 1996;46:5-27.
2. Woolf SH. Screening for prostate cancer with prostate-specific antigen. An examination of the evidence. *N Engl J Med* 1995;333:1401-5.
3. Ries LAG, Miller BA, Hankey BF, Kosary CL, Hara A, Edwards BK, editors. SEER cancer statistics review, 1973-1991: tables and graphs. Bethesda, Md: National Cancer Institute, 1994. (NIH publication no. 94-2789.)
4. Pienta KJ, Demers R, Hoff M, Kau TY, Montie JE, Severson RK. Effect of age and race on the survival of men with prostate cancer in the metropolitan Detroit tricounty area, 1973 to 1987. *Urology* 1995;45:93-101.
5. Albert DM, Rubenstein RA, Scheie HG. Tumor metastases to the eye. I. Incidence in 213 adult patients with generalized malignancy. *Am J Ophthalmol* 1967;63:723-6.
6. Goldberg RA, Rootman J, Cline RA. Tumors metastatic to the orbit: a changing picture. *Surv Ophthalmol* 1990;35:1-24.
7. Ferry AP, Font RL. Carcinoma metastatic to the eye and orbit. I. A clinicopathologic study of 227 cases. *Arch Ophthalmol* 1974;92:276-86.
8. Rose AM. Die orbita als absiedlungsort von malignomen. *Klin Monatsbl Augenheilkd* 1965;147:857.
9. Shields CL, Shields JA, Peggs M. Tumors metastatic to the orbit. *Ophthalm Plast Reconstr Surg* 1988;4:73-80.
10. Tijn J, Koornneef L, Eijpe A, Thomas L, Gonzalez DG, Veenhof C. Metastatic tumors to the orbit—management and prognosis. *Graefes Arch Clin Exp Ophthalmol* 1992;30:527-30.
11. Greenberg HS, Deck MD, Vikram B, Chu FC, Posner JB. Metastasis to the base of the skull: clinical findings in 43 patients. *Neurology* 1981;31:530-7.
12. Boldt HC, Nerad JA. Orbital metastases from prostate carcinoma. *Arch Ophthalmol* 1988;106:1403-8.
13. Carriere VM, Karcioglu ZA, Apple DJ, Insler MS. A case of prostate carcinoma with bilateral orbital metastases and the review of the literature. *Ophthalmology* 1982;89:402-6.
14. Sher JH, Weinstock SJ. Orbital metastasis of prostatic carcinoma. *Can J Ophthalmol* 1983;18:248-50.
15. Mashka DA, McCulloch TM, Nerad JA. Prostate cancer metastatic to the orbit. *Ann Otol Rhinol Laryngol* 1996;105:70-1.

16. Laine FJ, Kuta AJ. Imaging the sphenoid bone and basiocciput: pathological considerations. *Semin Ultrasound CT MR* 1993;14:160-77.
17. Khan AU, Greene LF, Neault RW. Orbital metastasis from prostatic carcinoma. *Int Surg* 1977;62:465-7.
18. Kopelman JE, Shorr N. A case of prostatic carcinoma metastatic to the orbit diagnosed by fine needle aspiration and immunoperoxidase staining for prostatic-specific antigen. *Ophthalmic Surg* 1987;18:599-603.
19. Ransom DT, Dinapoli RP, Richardson RL. Cranial nerve lesions due to base of the skull metastases in prostate carcinoma. *Cancer* 1990;65:586-9.
20. Mickel RA, Zimmerman MC. The sphenoid sinus: a site for metastasis. *Otolaryngol Head Neck Surg* 1990;102:709-16.
21. Henderson JW, Campbell RJ, Farrow GM, Garrity JA. *Orbital tumors*. 3rd ed. New York: Lippincott Raven Press, 1993.
22. Green S, Som PM, Lavagnini PG. Bilateral orbital metastases from prostate carcinoma: case presentation and CT findings. *AJNR Am J Neuroradiol* 1995;16:417-9.
23. Font RL, Ferry AP. Carcinoma metastatic to the eye and orbit. III. A clinicopathologic study of 28 cases metastatic to the orbit. *Cancer* 1976;38:1326-35.
24. Di Leo A, Bajetta E. Adenocarcinoma of unknown primary site with bone marrow and orbital metastases suggestive of a prostatic origin. *Tumori* 1992;78:63-4.
25. Moss HM. Expanding lesions of the orbit: a clinical study of 230 consecutive cases. *Am J Ophthalmol* 1962;54:761-70.
26. Silva D. Orbital tumors. *Am J Ophthalmol* 1968;65:318-39.
27. Reifler DM, Kini SR, Liu D, Littleton RH. Orbital metastasis from prostatic carcinoma. Identification by immunocytochemistry. *Arch Ophthalmol* 1984;102:292-5.
28. Zimmerman RA, Bilaniuk LT. Computed tomography of tumors of the sphenoid sinus and bone. *Adv Otorhinolaryngol* 1978;24:39-41.
29. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. *Cancer* 1985;55:1468-72.
30. Klein EA. An update on prostate cancer. *Cleve Clin J Med* 1995;62:325-38.
31. Defining and updating the American Cancer Society guidelines for the cancer-related checkup: prostate and endometrial cancers. *CA: Cancer J Clin* 1993;43:42-6.
32. US Preventive Services Task Force. *Guide to clinical preventive services*. 2nd ed. Baltimore: Williams & Wilkins, 1996.