CLINICAL VIGNETTE

Prostate Cancer Presenting as Diplopia

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A 64-year-old man with a history of alcohol dependence, hyperlipidemia, and chronic low back pain presented to primary care with diplopia for 2 days. Optometry evaluated the patient earlier that day and noted a right lateral rectus palsy. An MRI of the brain and orbit showed extensive metastatic osseous disease with involvement of the clivus and right cavernous sinus. Labs were notable for an elevated PSA of 954 ng/mL, alkaline phosphatase of 224 IU/L, GGT of 106 IU/L and LDH of 599 IU/L. The total protein was 7.8 g/dL with albumin 4.2 g/dL. Complete blood counts were mildly suppressed with WBC 5K/uL, hemoglobin 12.7 g/dL, platelet count 140k/ uL. Serum protein electrophoresis revealed a faint IgG-kappa monoclonal protein band in the in the gamma region. Serum kappa free light chains were elevated at 31.4 mg/L, and UPEP immunofixation showed no monoclonal band.

The patient was seen in oncology and reported decreased appetite and weight loss over the past year as well as urinary frequency and nocturia. The patient's wife also reported that her husband developed a "knot on the head" about 3 months prior to presentation. He denied fever, chills, or night sweats. Family history included stomach cancer in his father, but no history of prostate cancer. Subsequent prostate biopsy confirmed prostate adenocarcinoma with a Gleason score 4+4, and CT scans showed extensive retroperitoneal and pelvic lymphadenopathy as well as multiple areas of osseous metastasis including bilateral pathologic rib fractures and the right iliac bone. His new diplopia was attributed to the location of one of his metastases.

Discussion

The sixth cranial nerve (abducens nerve) innervates the ipsilateral lateral rectus muscle for eye abduction. The motoneurons of the nerve originate in the pons, course along the clivus, traverse the cavernous sinus (adjacent to the internal carotid artery and trigeminal nerve), and enter the orbit through the superior orbital fissure. Sixth cranial nerve palsy, also known as lateral rectus palsy or abducens nerve palsy, is the most common ocular cranial nerve palsy to occur in isolation and often presents with binocular horizontal diplopia.[1] The most common etiologies of sixth cranial nerve palsy are neoplasm, trauma (such as injuries of the base of the skull), vascular disease (including of the pons and internal carotid artery), and inflammation. Other etiologies include congenital causes, increased intracranial pressure which can increase traction of the sixth nerve, Wernicke encephalopathy, and giant cell arteritis (which can cause both unilateral and bilateral palsy).[2] Neuroimaging with contrast MRI of the brain and orbits is recommended to help elucidate the etiology especially when other neurologic findings accompany the diplopia, such as papilledema, nausea, vomiting, dysarthria, altered mental status, gait ataxia.

This patient's MRI showed lesions of the skull and skull base and an infiltrative mass in the region of the clivus, invading the cavernous sinus. The clivus, a bony inclined part of the posterior fossa, forms the anterior margin of the foramen magnum and is closely associated with the midbrain, pons, and medulla. The abducens nerve exits the brainstem at the pontomedullary junction and courses superiorly between the pons and clivus.[3] The most common primary neoplastic lesions in the clivus are chordomas and meningiomas; others include multiple myeloma and diffuse large B cell lymphoma.[4] Metastasis to the clivus is rare, estimated at approximately 0.02% of all intracranial tumors. A systematic review of metastatic lesions of the clivus reported, the most common primary cancer was prostate. Other sources included gastrointestinal, lung, kidney and liver, and less commonly breast, skin, thyroid, and uterine/cervix malignancies. The review noted that 70% of cases presented with abducens nerve palsy.[3] In addition to sixth cranial nerve palsy, metastatic prostate cancer to the skull base can cause cranial nerve III, V and VII palsies, with symptoms ptosis, difficulty closing the eye, and mouth drooping.[5]

Lesions of the clivus can sometimes be resected or decompressed using a number of surgical approaches, including endoscopic endonasal approaches craniotomy and microsurgical decompression, microscopic transsphenoidal approach, and maxillary osteotomy.[3]

Prostate cancer is the most common malignancy in males in the United States. Approximately 12.6% of men will be diagnosed with prostate cancer during their lifetime, and in 2019 more than 3.2 million men were living with prostate cancer in the United States. At the time of diagnosis, approximately 73% have localized cancer, 14% have regional lymph node involvement, and 7% have distant metastasized cancer.[6] The predominant site of metastasis for prostate cancer is bone and bone pain as the most common symptom.

Treatment of recurrent castration-sensitive prostate cancer (CSPC) depends on the extent of the disease. For patients with isolated biochemical recurrence, where there is an increase in

serum PSA but no evidence of local or disseminated disease, treatment can include local salvage therapy and/or androgen deprivation therapy (ADT). These treatments should be especially considered if there are high-risk features for early metastasis. These include a PSA doubling time <1 year, a pathologic Gleason score 8 to 10 after radical prostatectomy, clinical Gleason score 8 to 10 after radiation therapy, or an interval to biochemical recurrence <18 months.[7] For patients with locally advanced and metastatic recurrence, combination treatment of ADT with another systemic agent (i.e. abiraterone, enzalutamide, docetaxel) can help with palliation of symptoms and to reduce severe complications, such as pathologic fractures and spinal cord compression.

ADT can be accomplished by either surgical or medical castration. Medical castration utilizes gonadotropin-releasing hormone (GnRH) agonists (i.e. leuprolide) and GnRH antagonists (i.e. degarelix, relugolix) to decrease testicular production of testosterone through its effects on the hypothalamic-pituitary axis. Adverse effects of ADT include decreased libido, erectile dysfunction, gynecomastia, hot flashes, decreased bone mineral density with increased fracture risk, and changes in mood or cognition.[8] At the start of treatment, GnRH agonists cause an initial transient surge of luteinizing hormone and subsequent increase in testosterone ("tumor flare" or "flare phenomenon"), which may worsen symptoms of bone pain, urinary obstruction, and spinal cord compression. The use of a first-generation nonsteroidal antiandrogen (i.e. bicalutamide, flutamide) prior to starting ADT can help minimize the potential "flare" symptoms.[9]

For patients with locally advanced and metastatic recurrence, ADT can be combined with other systemic agents. Abiraterone (plus prednisone) blocks the intracellular conversion of androgen precursors in the testes, adrenal glands and prostate tumor tissue. Enzalutamide functions as an androgen receptor inhibitor. ADT combined with docetaxel-based chemotherapy has shown benefit in patients with high-volume disease (HVD), which is defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis; some patients may not be candidates for docetaxel due to its myelosuppression and subsequent increased risk of infections.[10]

Case Outcome

The patient was initially started on bicalutamide for seven days, followed by leuprolide injections every three months as well as oral abiraterone and prednisone. One month after starting treatment serum PSA had decreased to 86.75 ng/mL and total testosterone was <10 ng/dL. After 6 months, the serum PSA was undetectable (<0.1 ng/mL) and his diplopia resolved.

The patient tolerated treatment with bicalutamide, leuprolide, and abiraterone plus prednisone very well. He was able to maintain his activities of daily living, including a multi-state road trip with his wife, with few complications. Two months after starting treatment, the patient reported new upper and mid-back pain. Imaging showed T6/T7 and T12/L1 vertebral fragility fractures and was started on annual intravenous bisphosphonate. He was seen by Pain Management, Palliative Care, and Acupuncture for related pain only. He required a short course of opiate analgesics as the pain was well-controlled with duloxetine and acupuncture. Prior to treatment, the patient's exercise regimen included frequent walking, aquatic exercises, and weight resistance. By six months of treatment, the patient was able to resume much of his exercise routine.

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